

**AN IMPROVED METHOD FOR THE STILBENES SYNTHESIS
VIA THE HECK REACTION AND APPROACH
TO INDOLE SYNTHESIS USING PIDA**

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Abstract

Six iodoanilides incorporating different amide functionalities (e.g butyramide, furan carboxamide, cyclohexylamide, (**2.1** to **2.6**)) were prepared by established methods. These iodocarboxamides were transformed to the corresponding amido stilbenes (**2.5** to **2.12**) by an improved Heck procedure. Following silica gel chromatography, the resulting stilbene orthocarboxamides were exposed to diacetoxy iodobenzene with a view to indole synthesis.

Abstrak

Enam iodoanilida bergabung dengan amida yang berbeza (seperti butiramida, furan karboksamida, sikloheksilamida (**2.1-2.6**)) dengan kaedah yang sedia ada. Dengan menggunakan kaedah Heck yang telah diperbaiki, semua iodokarboksamida ini akan bertindak balas menjadi amido stilbene (**2.8-2.13**). Selepas ditulen dengan kromatografi gel silika, stilbene ortokarboksamida didedahkan kepada diasektoksi iodobenzena untuk menghasilkan indole (**2.14**).

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List of Abbreviations

<i>n</i> -BuLi	<i>n</i> -Butyllithium
<i>t</i> -Bu	<i>tert</i> -Butyl
<i>t</i> -BuLi	<i>tert</i> -Butyllithium
<i>Ac</i>	Acetyl
<i>Ac</i> ₂ <i>O</i>	Acetic anhydride
<i>Bn</i>	Benzyl
<i>Boc</i>	<i>t</i> -Butoxycarbonyl
<i>Bu</i>	Butyl
<i>Bu</i> ₃ <i>N</i>	Tributylamine (TBA)
<i>Bz</i>	Benzoyl
<i>Cat</i>	Catalytic
<i>CBz</i>	Carbobenzyloxy
<i>CF</i> ₃	Trifluoromethyl
<i>CH</i> ₃ <i>CN</i>	Acetonitrile
<i>CH</i> ₂ <i>Cl</i> ₂	Dichloromethane
<i>DDQ</i>	2,3-Dichloro-5,6-dicyanobenzoquinone
<i>DMA</i>	<i>N,N</i> -Dimethylacetamide
<i>DMAP</i>	2,4-Dimethylaminopyridine
<i>DMEDA</i>	<i>N,N'</i> -dimethylethylenediamine

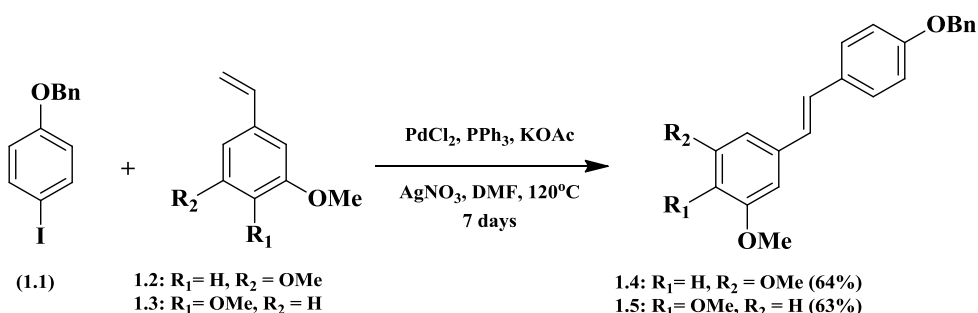
<i>DMF</i>	<i>N,N</i> -Dimethylformamide
<i>Et</i>	Ethyl
<i>Et₂O</i>	Diethyl ether
<i>EtOH</i>	Ethanol
<i>Et₃N</i>	Triethylamine (TEA)
<i>EDG</i>	Electron donating group
<i>EWG</i>	Electron withdrawing group
<i>FeCl₃</i>	Iron(III) chloride
<i>HRMS</i>	High resolution mass spectroscopy
<i>IC₅₀</i>	Half maximal inhibitory concentration
<i>LC</i>	Liquid chromatography
<i>Me</i>	Methyl
<i>MeOH</i>	Methanol
<i>Mn(OAc)₃</i>	Manganese(III) acetate
<i>MS</i>	Mass chromatography
<i>m.p.</i>	Melting oint
<i>NQO1</i>	NAD(P)H dehydrogenase quinone 1
<i>NMR</i>	Nuclear mangnetic resonance
<i>Nu</i>	Nucleophile
<i>Pd</i>	Palladium
<i>Pd(OAc)₂</i>	Palladium(II) acetate

<i>Pd₂(dba)₃</i>	Tris(dibenzylidene acetone)dipalladium(0)
<i>Ph</i>	Phenyl
<i>PIDA</i>	Phenyliodine(III) diacetate
<i>PIFA</i>	Phenyliodine bis(trifluoroacetate)
<i>PPh₃</i>	Triphenylphosphine
<i>r.t</i>	Room temperature
<i>THF</i>	Tetrahydrofuran
<i>TLC</i>	Tin layer chromatography
<i>TMEDA</i>	Tetramethylethylenediamine
<i>Ts</i>	Tosyl

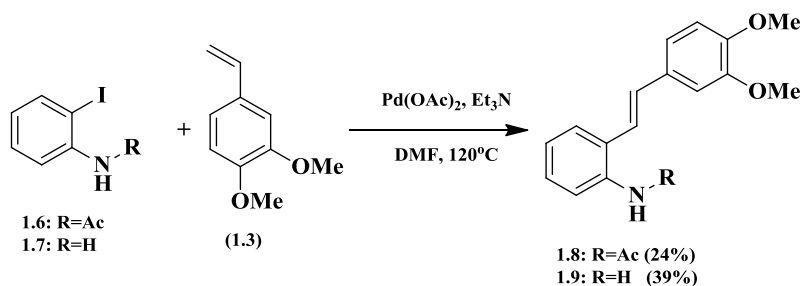
Chapter 1

1.1 Introduction

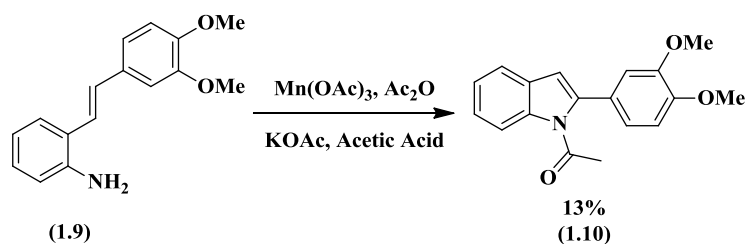
In 2002, our group described the construction of stilbenes **1.4** and **1.5** by the Heck procedure in good yield (**Scheme 1.1**) (Thomas *et al.*, 2002). Two years later, ortho-amido stilbenes **1.8** and **1.9** were constructed from another Heck coupling (**Scheme 1.2**) (Thomas *et al.*, 2004). However, in-contrast to the chemistry in **Scheme 1.3**, the 3,4-dimethoxy-10-acetamido stilbene **1.8** (**Scheme 1.4**), when exposed to FeCl₃ gave rise to, the indoline **1.11** and the bisindoline **1.12** were formed in yields of 37% and 11% respectively. The indole was not observed (Kee *et al.*, 2011; Thomas *et al.*, 2008).



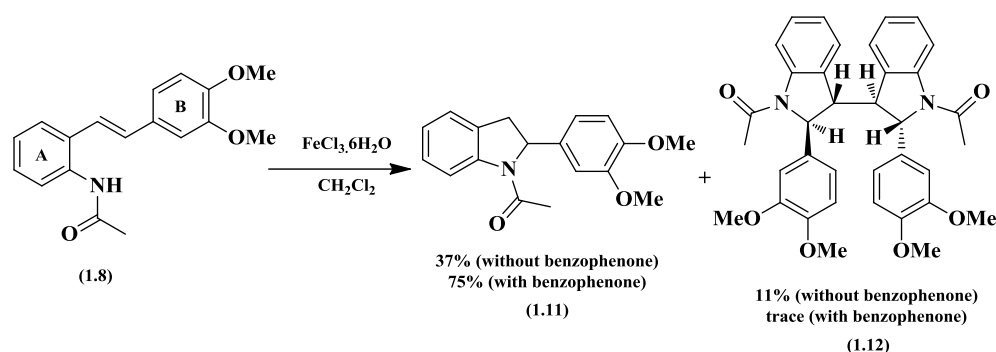
Scheme 1.1: Original stilbene synthesis (Thomas *et al.*, 2002)



Scheme 1.2: Construction of the ortho-amido stilbenes (**1.8**, **1.9**) by the Heck procedure (Thomas *et al.*, 2004)



Scheme 1.3: Manganese triacetate promoted indole construction (Thomas *et al.*, 2004)



Scheme 1.4: FeCl₃ oxidative coupling of acetamido stilbene (Kee *et al.*, 2011; Thomas *et al.*, 2008)

More recently fourteen novel stilbene carboxamides were prepared by the Heck procedure and a substantial proportion of these were biologically evaluated for cytotoxic and chemopreventive activity against several cancer cell lines including the HT₂₉ colon cancer cell line (Kee *et al.*, 2010). It is interesting to observe that the stilbene (**1.13**) incorporating the furan carboxamide and possessing 3,5-dimethoxy substitution showed intriguing chemopreventive activity against WRL-68 fetal hepatocytes with elevation of NAD(P)H: quinone oxidoreductase 1 (NQO1). Interestingly, resveratrol required a concentration five times higher than that of **1.13** to produce the same elevation of NQO1.

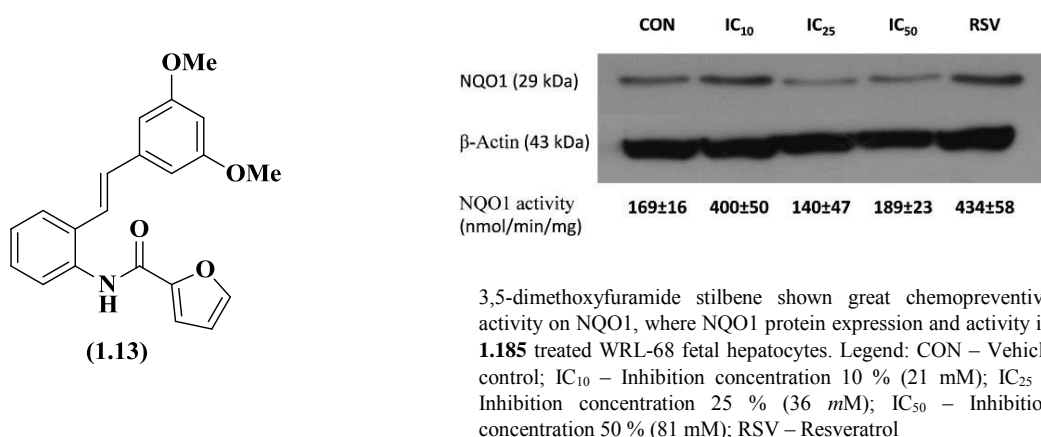
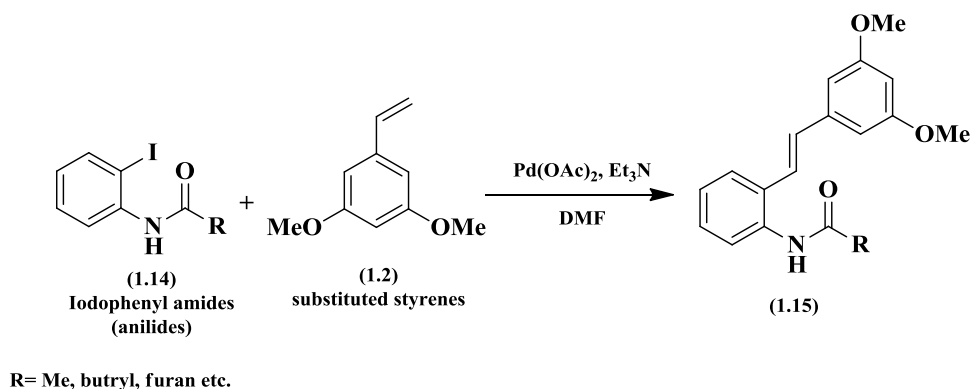


Figure 1.1: 3,5-dimethoxyfuranamide stilbene and its NQO1 result (Kee *et al.*, 2010)

1.2 Study Objective

In the light of the above, we decided to focus on the following objectives which were:

1. to synthesize stilbene analogues with structurally different amide moieties but retaining the 3,5-dimethoxy substitution pattern, by the Heck reaction (**Scheme 1.6**), and to study the reaction (**Scheme 1.2**) with a view to optimizing the yield especially of 3,5-dimethoxy-10-furancarboxamido stilbene **1.13** that showed a significant level of NQO1 activity previously described.



Scheme 1.5: The Heck Reaction

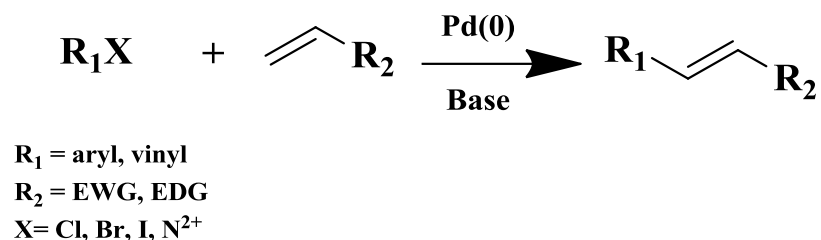
2. to subject the stilbenes to oxidative conditions promoted by iodobenzene diacetate through the formation (we presume) of the nitrenium ion intermediate (in contrast to FeCl_3 promoted reactions) to construct the indole skeleton.

1.3 Stilbenes and the palladium mediated coupling

1.3.1 Heck Reaction

$\text{Pd}(0)$ -mediated C-C coupling of an aryl or vinyl halide or sulfonate, in the presence of base to an alkene is referred to as the Heck reaction. The reaction was named after the winner of the 2010 Nobel Prize in chemistry Richard F. Heck who was responsible for this epoch making event in olefin construction first reported in 1972 and later extended to other systems (**Scheme 1.6**) (Heck and Nolley, 1972). Heck chemistry is flexible, adaptable and expandable. It is known that by varying the

conditions such as temperature, ligand, the nature of base, solvent, substrate structure, a change in reaction profile from “unheckable” to “heckable” is possible.



Scheme 1.6: Heck reaction scheme

1.3.2 Biologically Active Stilbenes

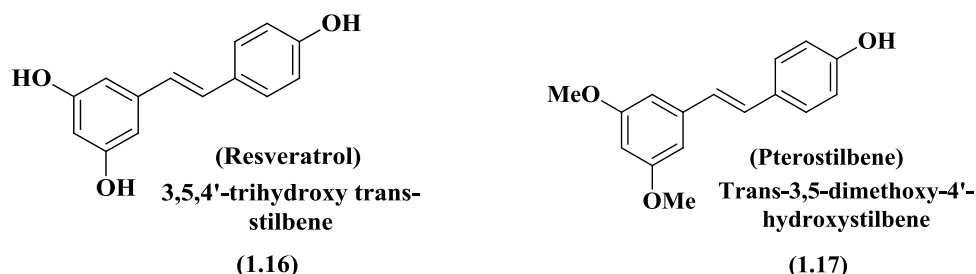


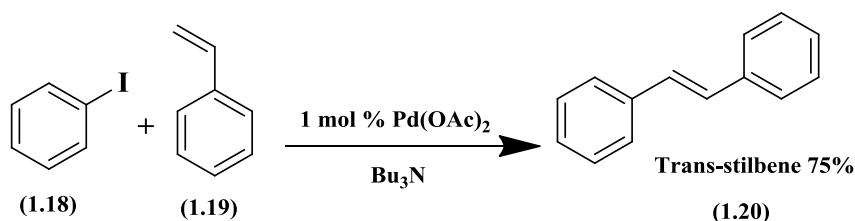
Figure 1.2: Biologically active stilbene derivatives

3,5,4'-trihydroxy *trans*-stilbene (resveratrol, **1.16**), is a naturally occurring phytoalexin and one of the most important stilbene derivatives and present in various foods such as grapes, peanuts, red wine and berries and other food products/plants. Resveratrol shows antioxidant/anti-mutagenic, anti-inflammatory activity and is a potent chemopreventive agent for human breast cancer, oral squamous carcinoma, promyelocytic leukaemia and prostate cancer (Lee *et al.*, 2004; Roberti *et al.*, 2003; Waffo-Tégou *et al.*, 2001). [In the French paradox, which is the observation of the low incidence of coronary heart disease among French people compared to the American's for example, it is resveratrol's a potent anti-platelet aggregation properties which are responsible for this phenomenon (Chen *et al.*, 2009; Frémont, 2000).]

Trans-3,5-dimethoxy-4'-hydroxystilbene (**1.17**), also called as pterostilbene, is found in blueberries and grapes. Pterostilbene shows better cell viability and lower IC₅₀ values (2-5 fold lower) than resveratrol, which may due to better systemic bioavailability as well as to the presence of two methoxy groups that renders it lipophilic. Pterostilbene in serum has a longer half-life (105 min) compared to resveratrol (14 min). It shows superior chemopreventive activity and better anti-inflammatory properties for e.g. prostate cancer, human colon cancer cells, and human gastric carcinoma cells (Lin *et al.*, 2012; Nutakul *et al.*, 2011; Rimando *et al.*, 2002). Pterostilbene also demonstrates better antioxidant activity via peroxy-radical scavenging activities compared to resveratrol with $237 \pm 58 \mu\text{M}$ and $253 \pm 53 \mu\text{M}$ respectively.

1.3.3 Stilbenes and the Heck Reaction

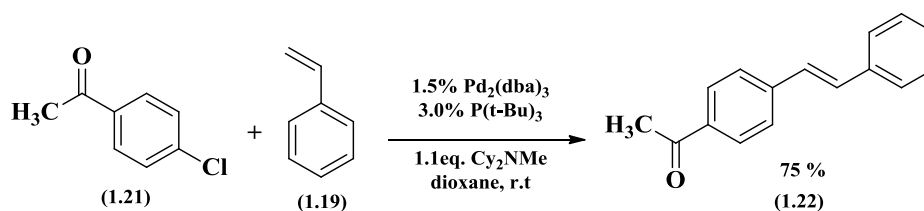
In 1972, Richard F. Heck reported the first stilbene to be synthesized by the Heck reaction using palladium acetate (Pd(OAc)₂) in the presence of Bu₃N base. Iodobenzene (**1.18**) and the styrene (**1.19**) were reacted together in the absence of solvent in a steam bath to produce *trans*-stilbene (**1.20**) in 75% yield (**Scheme 1.7**) (Heck and Nolley, 1972).



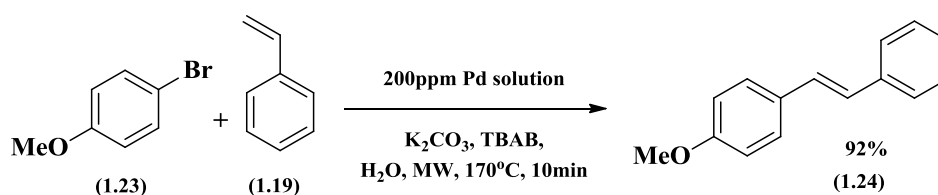
Scheme 1.7: First stilbene synthesized via the Heck reaction (Heck and Nolley, 1972)

For the efficient synthesis of stilbenes by the Heck reaction, a number of parameters need to be controlled. Littke and Fu (2001) reported the synthesis of para-acetylstilbene by exposure of parachloroacetophenone (**1.21**) to the styrene in the

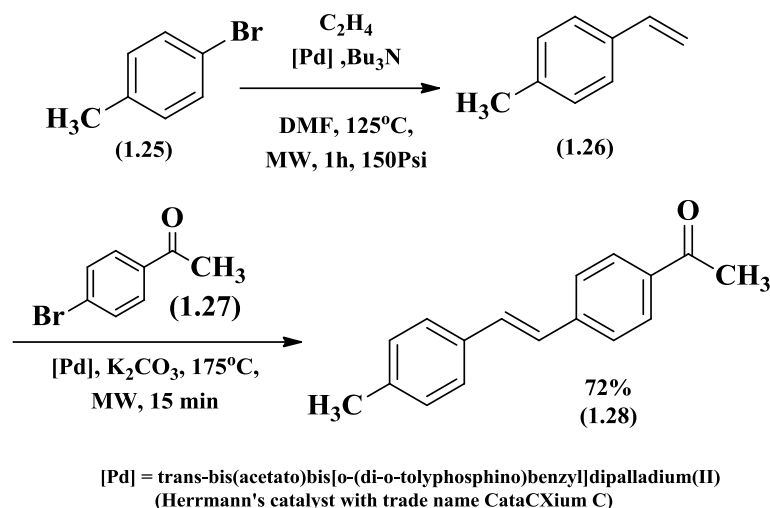
present of $\text{Pd}_2(\text{dba})_3$ / $\text{P}(t\text{-Bu})_3$ (**Scheme 1.7**). Tetrabutylammonium bromide (TBAB) is another ligand for the Heck construction of stilbenes. Arvela and Leadbeater (2005) reported the microwave assisted stilbene construction promoted by palladium solution and TBAB in water, thus 1-bromo-4-methoxybenzene (**1.23**) reacted with styrene (**1.19**) to produce the methoxy-stilbene (**1.24**) in excellent yield (**Scheme 1.9**). Subsequently, Leadbeater and Kormos (2008) reported a unique one-pot two step double microwave promoted Heck construction thus 1-bromo-4-methylbenzene (**1.25**) was first converted into 4-substituted styrene (**1.26**) followed by second Heck reaction to give the nonsymmetrically substituted stilbene (**1.28**) in the presence of Herrmann's catalyst- CaraCXium C-palladium catalyst (*trans*-bis(acetato)bis[*o*-(*di*-*o*-tolylphosphino)benzyl]dipalladium(II)) (**Scheme 1.10**).



Scheme 1.8: Stilbene synthesis using $\text{Pd}_2(\text{dba})_3/\text{P}(t\text{-Bu})_3$ (Littke and Fu, 2001)

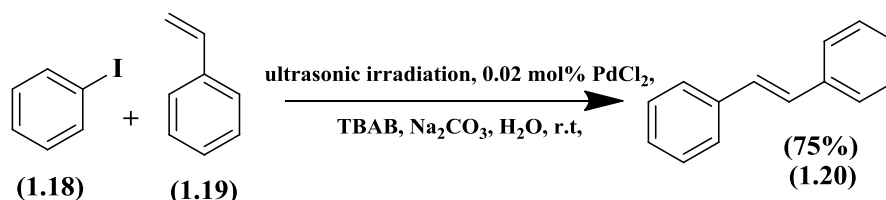


Scheme 1.9: Microwave assisted stilbene construction (Arvela and Leadbeater, 2005)



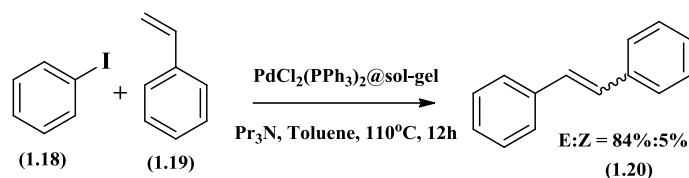
Scheme 1.10: Stilbene synthesis using Herrman catalyst (Kormos and Leadbeater, 2008)

Another approach to Heck-stilbene construction was reported by Zhang et al. (2006) in which ultrasonic irradiation was employed. In the presence of a palladium catalyst, a TBAB ligand and Na_2CO_3 in water, iodobenzene reacted with the styrene to give the stilbene in 75% yield (**Scheme 1.11**).

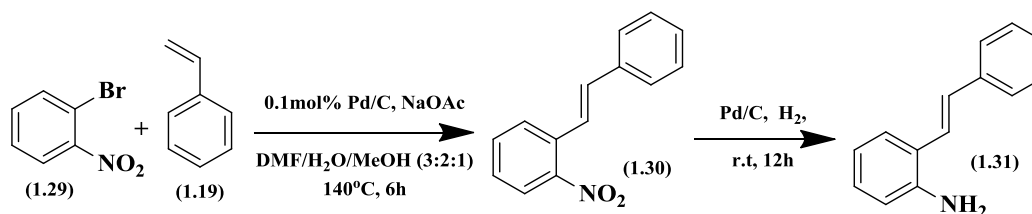


Scheme 1.11: Ultrasonic assisted stilbene synthesis (Zhang and Wang, 2006)

Although palladium heterogeneous catalysts perform well for the stilbene synthesis, the industrial applications are limited due to the high cost and the recycling problem. Therefore many inorganic solid-supported (e.g. carbon and sol-gel) and polymer-supported heterogeneous palladium reagents have been developed. Hamza and co-workers (2004) have employed the $\text{PdCl}_2(\text{PPh}_3)_2$ impregnated on a silica sol-gel homogeneous catalyst (**Scheme 1.12**), while Gruber's group (2004) have exploited palladium on activated carbon (**Scheme 1.13**)

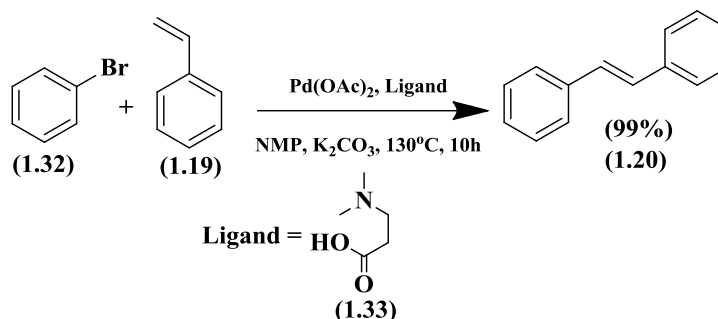


Scheme 1.12: Stilbene synthesis in sol-gel (Hamza *et al.*, 2004)

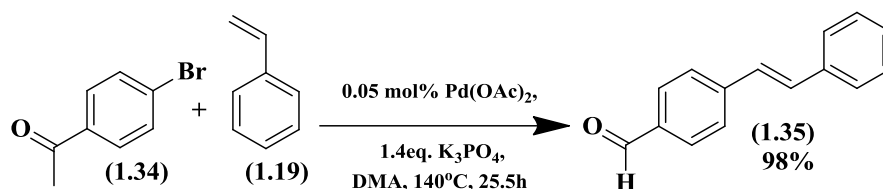


Scheme 1.13: Stilbene synthesis on activated carbon (Gruber *et al.*, 2004)

Phosphine ligands, which have traditionally been employed in the Heck reaction, are being replaced because of their cost, air-sensitivity and toxicity. Ligand free Heck reactions, have also been investigated. A good example of a phosphine-free Heck reaction is Cui *et al.*'s (2006) construction of the stilbene (1.20) by reacting bromobenzene (1.32) with the styrene (1.19) in the presence of palladium acetate, K_2CO_3 and the ligand *N,N*-dimethylglycine (1.21) (Scheme 1.14). Yao *et al.* (2003) reported a ligand free Heck reaction by using palladium acetate and a K_3PO_4 base in *N,N*-dimethylacetamide (DMA) solvent to give the stilbene in 98% yield (Scheme 1.15).

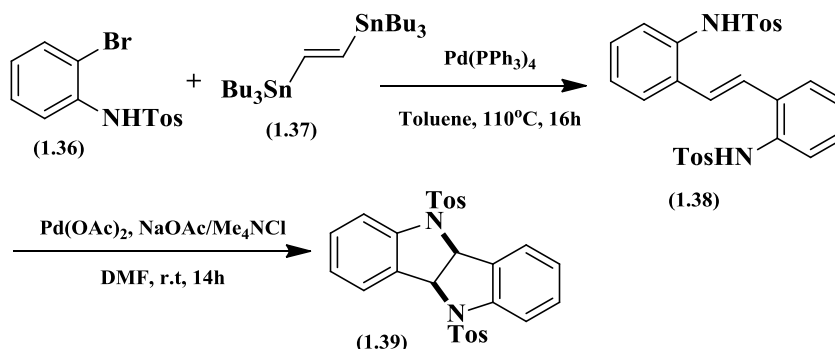


Scheme 1.14: Cui *et al.* and his ligand free stilbene synthesis (Cui *et al.*, 2006)

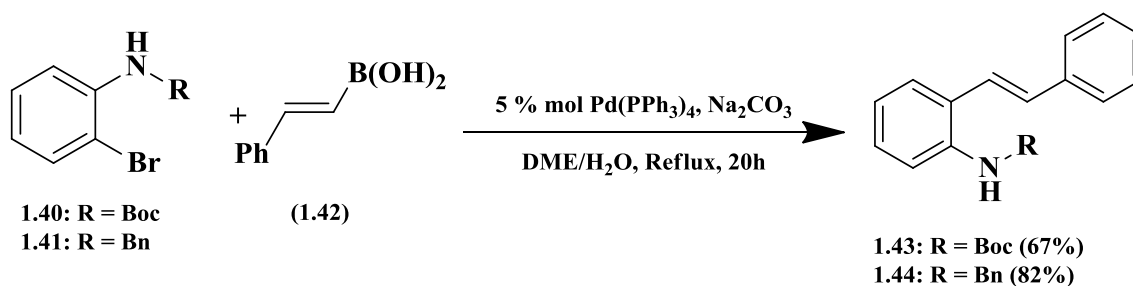


Scheme 1.15: Yao *et al.* and his ligand free stilbene synthesis (Yao *et al.*, 2003)

Muñiz (2007) reported the synthesis of *o*-diamidostilbene **1.38** through palladium catalysis (the Stille coupling). The stilbene thus generated was subsequently transformed into bisindoline **1.39** (Scheme 1.16). Hogan and O'Shea (2007) reported the synthesis of *o*-aminostilbenes **1.44** and **1.45** by using a stereoselective Suzuki-Miyaura cross-coupling of bromoamide and styrylboronic acid in moderate yield (Scheme 1.17). This construction was exploited in a quinoline syntheses. The Heck, Stille and Suzuki-Miyaura coupling all involve palladium catalysis

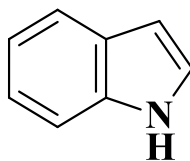


Scheme 1.16: Stille coupling *o*-amidostilbene synthesis (Muñiz, 2007)



Scheme 1.17: Suzuki-Miyaura cross-coupling approach to the *o*-amidostilbene (Hogan and O'Shea, 2007)

1.4.0 The Indole Ring Sytem



Indole (1.45)

Indole (1.45) – is a bicyclic heterocycle which contains a pyrrole ring fused at its α,β -position to a benzene ring where the pyrrole ring and benzene ring share one double bond. The indole moiety can be found in many natural products such as fungal metabolites, marine natural product and indole alkaloids. The indole ring system has become an important entity in many pharmaceutical agents and natural products, and hence, various reviews have appeared describing these biologically active indole alkaloids from either the synthetic point of view (Humphrey and Kuethe, 2006; Taber and Tirunahari, 2011) or from the standpoint of bioactivity involving indole derivatives (Sharma *et al.*, 2010). Synthetic methods employed in indole synthesis can be classified into nine types as shown in **Fig. 1.3** below:

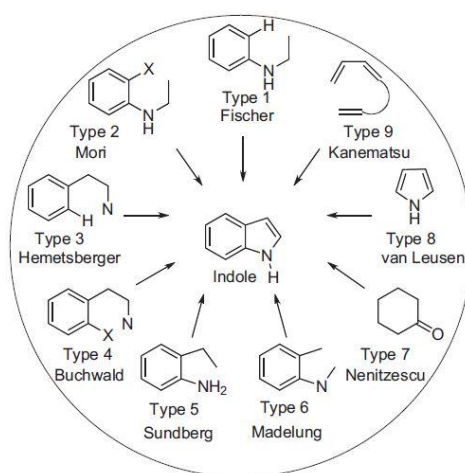
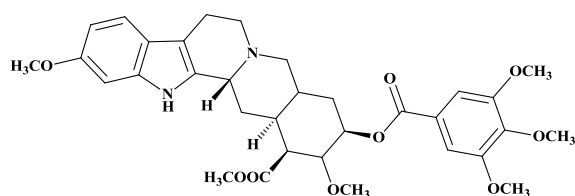


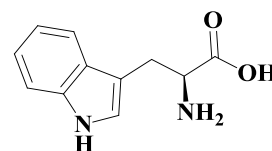
Figure 1.3: The nine types of indole synthesis (Taber and Tirunahari, 2011)

1.4.1 Biologically Active Indoles

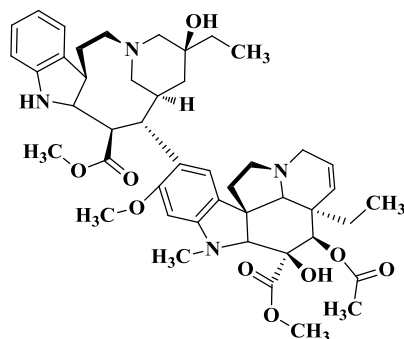
Indole natural products derivatives have shown some interesting biological activities which are clinically useful such as: yohimbine **1.46** (treatment of erectile dysfunction), tryptophan **1.47** (the biogenetic precursor for the synthesis of carbazomycin-B, which possesses anti-yeast activity, serves as a weak antibacterial and 5-lipoxygenase inhibitor, as well as an inhibitor for free radical induced lipid peroxidation) vinblastine **1.48** and vincristine **1.49** (treatment of leukaemia, Hodgkin's lymphoma, testicular cancer) (Clive *et al.*, 1993; Jürgens *et al.*, 2010; O'Connor and Maresh, 2006; Pollier *et al.*, 2011; Siles *et al.*, 2008).



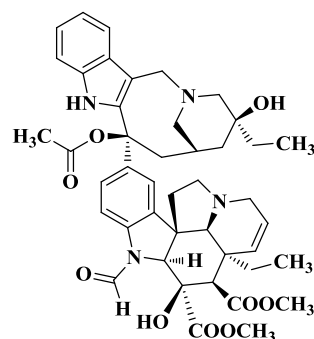
Yohimbine (**1.46**)



Tryptophan (**1.47**)



Vinblastine (**1.48**)



Vincristine (**1.49**)

1.4.2 Indole Synthesis

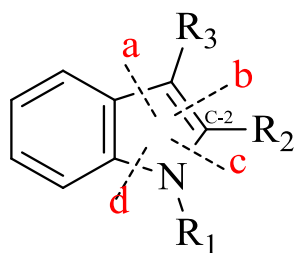


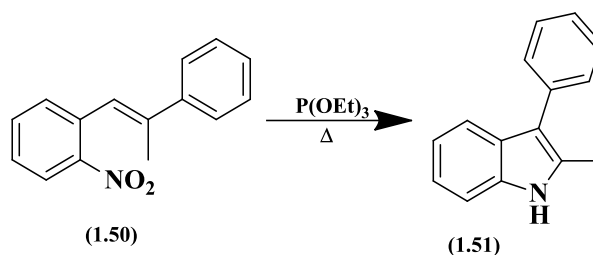
Figure 1.4: Possible disconnection of the indole ring

The synthesis of indoles can be classified according to four strategies as shown in Fig.

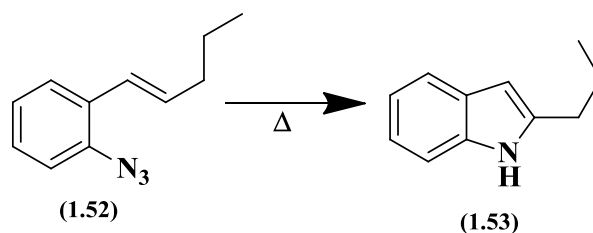
1.4:

- Formation of C-C bonds towards the benzene ring (the Fisher indole syntheses)
- route a
- From amides via ortho metallation and intramolecular nucleophilic attack (the Madelung indole syntheses) - route b
- Formation of C-N bonds between the aniline and carbon C-2 for cyclization (the Sundberg indole syntheses) - route c
- Formation of bond between nitrogen toward the benzene ring (the Hemestsberger and Buchwald indole syntheses) - route d

The retro-synthetic route c was first reported by Richard J. Sundberg in year 1967. The indole was synthesized via heating of α -Methyl-2'-nitrostilbene (**1.50**) with P(OEt)₃ (**Scheme 1.18**) (Sundberg and Yamazaki, 1967). Two years later, Sunberg *et al.* (1969) reported that the heating of (*E*)-1-(*o*-azidophenyl)pent-1-ene (**1.52**) produced the 2-substituted indole **1.53** as shown in **Scheme 1.19** (Sundberg *et al.*, 1969).

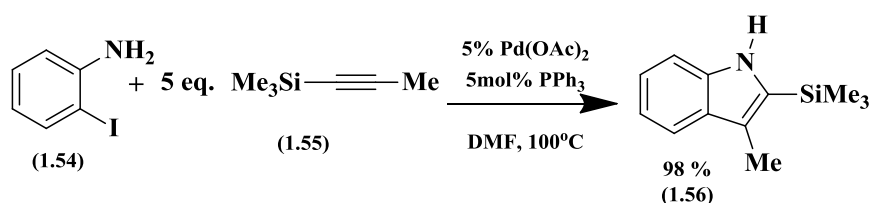


Scheme 1.18: First indole synthesized by Sundberg and Yamazaki (1967)

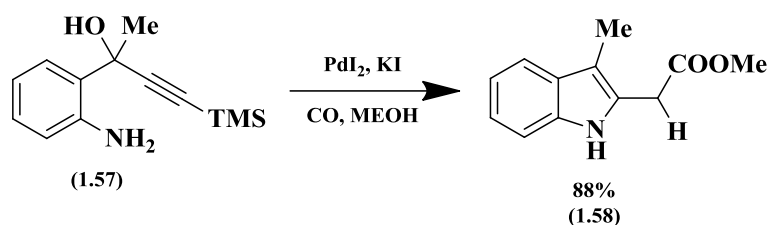


Scheme 1.19: Second indole syntheses by heating only (Sundberg *et al.*, 1969)

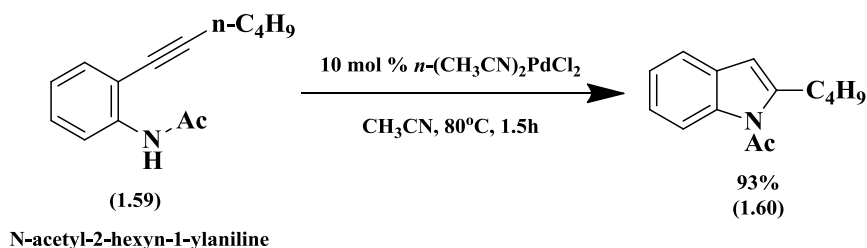
Catalysts based on transition metals such as palladium and copper have been applied to indole syntheses. Larock and co-workers (1998) reported the Pd^{2+} catalysed coupling of *o*-iodoaniline (**1.54**) to 2,3-disubstituted acetylenes (**1.55**) (incorporating the Me_3Si group) to produce 2-trimethylsilyl substituted indole **1.56** in excellent yield (**Scheme 1.20**) (Larock *et al.*, 1998). Gabriele *et al.* (2008) reported that, in the presence of the combination of PdI_2 , KI and carbon monoxide, 2-(2-aminophenyl)-4-(trimethylsilyl)but-3-yn-2-ol (**1.57**) underwent cyclisation to produce indole-2-acetic ester **1.58** in 88% yield via a 5-*exo-dig* ring closure (**Scheme 1.21**). As shown in **Scheme 1.22**, Rudisill and Stille (1989) converted *N*-acetyl-2-hexyn-1-ylaniline (**1.59**) into the 2-substituted indole **1.60** in 93% yield. The cyclization proceeds by nucleophilic attack of the acetamide on the Pd-complexed alkyne.



Scheme 1.20: Alkyne indole synthesis (Larock *et al.*, 1998)

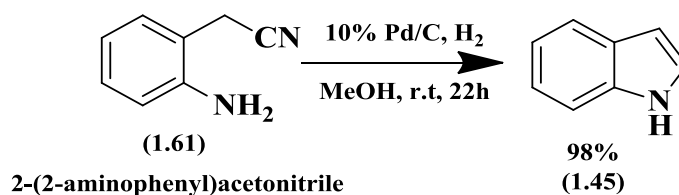


Scheme 1.21: 5-*exo-dig* indole synthesis (Gabriele *et al.*, 2008)

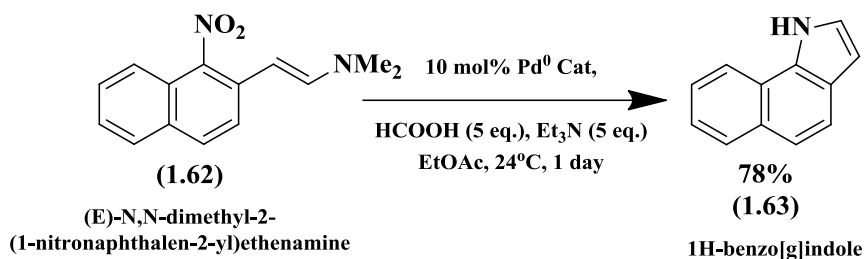


Scheme 1.22: Nucleophilic attack cyclization indole synthesis (Rudisill and Stille, 1989)

The use of Pd/C catalyst provides an alternative method for the synthesis of indoles. Sajiki and co-worker (2004) starting from, 2-(2-aminophenyl)acetonitrile (**1.61**), the intramolecular nucleophilic attack of the amino group on the nitrile in the presence of Pd on carbon to produce the indole (**1.45**) in 98% yield (**Scheme 1.23**). This successful syntheses were extended to the 1H-benzo[*g*]indole (**1.63**) by using an encapsulated nanoparticulate Pd-catalyst in the presence of the starting material (*E*)-*N,N*-dimethyl-2-(1-nitronaphthalen-2-yl)ethenamine (**1.62**) (**Scheme 1.24**).

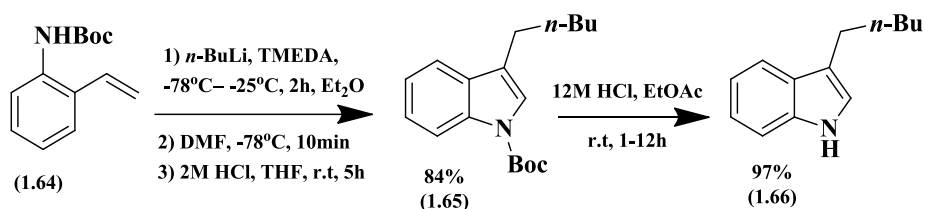


Scheme 1.23: Pd/C indole synthesis (Sajiki *et al.*, 2004)

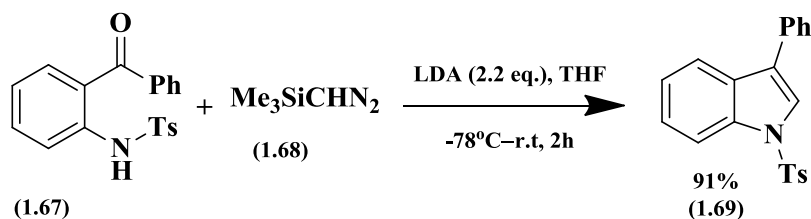


Scheme 1.24: Pd-nanoparticle catalyst indole synthesis (Siu *et al.*, 2004)

O'Shea and Coleman (2003) reported the use of *n*-BuLi for indole construction. The Boc-protected vinylaniline was converted into Boc-protected indole in three steps with *n*-BuLi and TMEDA base involved in the first step, followed by a deprotection to give the indole **1.66** (Scheme 1.25). A year later, Miyagi *et al.* (2004) used lithium trimethylsilyldiazomethane (TMSC(Li)N₂), which was generated in-situ by reaction of lithium diisopropylamide (LDA) and trimethylsilyldiazomethane (TMSCHN₂) (**1.68**). When *o*-tosylaminobenzophenone (**1.67**) was exposed to (TMSC(Li)N₂) in TMEDA/DMF, the 3-phenyl indole **1.69** was obtained in 91% yield (Scheme 1.26).



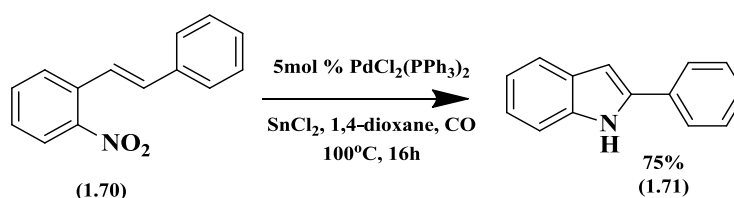
Scheme 1.25: 3-substituted indole synthesis (Coleman and O'Shea, 2003)



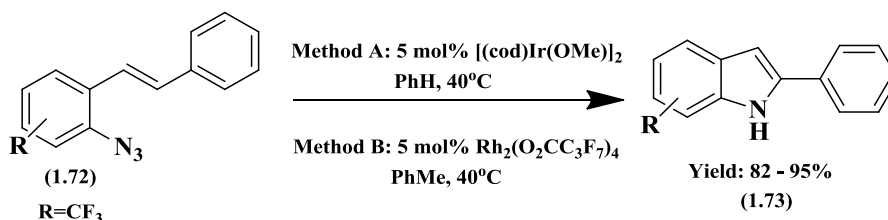
Scheme 1.26: Miyagi's indole synthesis (Miyagi *et al.*, 2004)

The Akazome's group and Sun's group have independently reported that indoles can be synthesized from the stilbenes by mean of the transition metals based on palladium, iridium and rhodium. Akazome and co-workers (1994) by exploiting

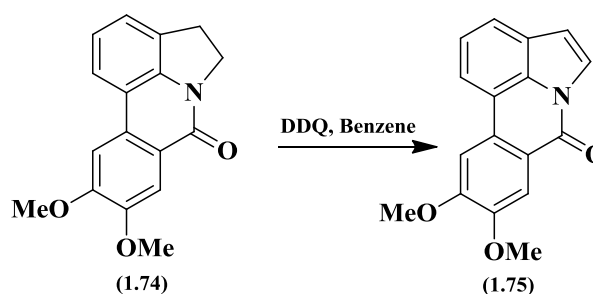
dichlorobis(triphenylphosphine)palladium ($\text{PdCl}_2(\text{PPh}_3)_2$)- tin(II) chloride (SnCl_2) catalytic system were able to generate indole in the presence of carbon monoxide. Under these conditions, the nitro group of 2-nitrostilbene (**1.70**) is deoxygenated prior to cyclisation to produce 2-phenylindole (**1.71**) in 75% yield. The reaction is thought to proceed via a nitrene intermediate (**Scheme 1.27**). In the method of Sun *et al.* (2009), the iridium(I) complex plays a critical role (method A). In method B, the rhodium complex is exploited, both methods producing the indole (82-95% yield). These syntheses are effective even with powerful electron-withdrawing groups like CF_3 (in various positions) (**Scheme 1.28**). Year 2005, Ganton and Kerr described an indole construction via the indoline (**Scheme 1.29**).



Scheme 1.27: Pd catalysed indole synthesis (Akazome *et al.*, 1994)



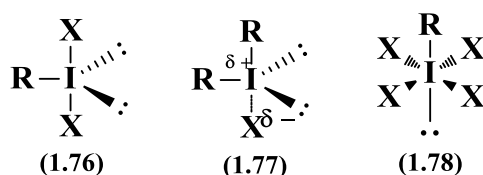
Scheme 1.28: Iridium and rhodium catalysed indole synthesis (Sun *et al.*, 2009)



Scheme 1.29: Indole syntheses via the indolines (Ganton and Kerr, 2005)

1.5.0 Polyvalent Iodine

Since the German chemist Willegerodt prepared the PhICl_2 as the first polyvalent organic iodine compound in 1886, the preparation and investigation of the chemistry polyvalent iodine has grown rapidly. Iodine(III) has chemical properties similar to heavy metals such as Hg(II) , Ti(III) and Pb(IV) but is more environmental friendly (Stang and Zhdankin, 1996). For these reasons polyvalent iodine compounds have attracted the attention of organic chemists. Organic polyvalent iodine derivatives can be categorized as of two types according to their structures: Firstly, iodine(III) compounds **1.97** and **1.98** which according to IUPAC recommendations are referred to as λ^3 -iodanes, and secondly, the λ^5 -iodanes or iodine(V) compounds, e.g. **1.99**.



R= carbon ligand; X= halogen, O-, or N-ligand

Figure 1.5: Organic polyvalent iodine derivatives

1.5.1 Hypervalent Iodine

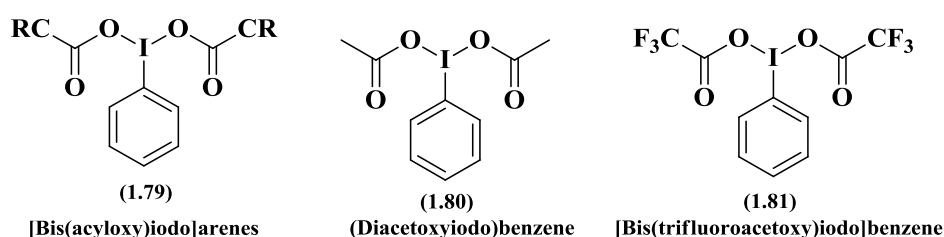


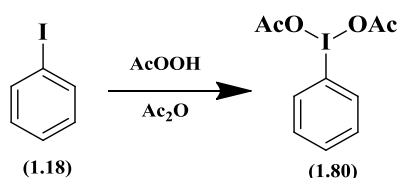
Figure 1.6: Hypervalent iodine derivatives

[Bis(acyloxy)iodo]arenes ($\text{ArI}(\text{O}_2\text{CR})_2$, λ^3 -iodanes compounds, are generally colorless crystals that are stable at room temperature. They are the most well investigated and useful iodine(III) polyvalent iodine compounds. Hypervalent iodine compounds are highly electrophilic due to the existence of the linear three-center

covalent bonds between iodine and two acetoxys group (refer to structure **1.76**) (Zhdankin and Stang, 2008). [Bis(trifluoroacetoxy)iodo]benzene (BTI), alternatively named as phenyliodine(III) bis(trifluoroacetate) (PIFA) and (diacetoxyiodo)benzene (DIB/DAIB) also called phenyliodine diacetate (PIDA), are two examples of commercially available hypervalent iodine compounds that are commonly used as oxidizing agents as starting materials for the preparation of other iodine(III) compounds, and also as radical initiators. Hypervalent iodine reagents are environmentally friendly, require mild reaction conditions, are stable in the presence of moisture and oxygen, and possess high efficiency and oxidative selectivity. For these reasons they are among the most popular reagents in organic synthesis.

1.5.2 Phenyliodine Diacetate

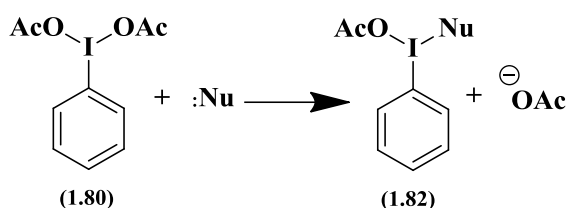
Phenyliodine(III) diacetate (PIDA) (**1.80**), a well investigated iodine(III) organic compound, can be prepared by an oxidative reaction between iodobenzene and $\text{H}_2\text{O}_2/\text{AcOH}/\text{Ac}_2\text{O}$ (**Scheme 1.30**).



Scheme 1.30: Phenyliodine(III) diacetate synthesis

PIDA is an efficient replacement for some toxic heavy metals, such as: lead(IV)-, mercury(II)-, cadmium(IV)-, and thallium(III)-based oxidizing agents that can produce high purity products, which are especially important in the pharmaceutical industry. The ability to undergo ligand exchange reactions similar to heavy metal with various nucleophiles (PhIOAc group can first react as nucleophile and is later transformed into leaving group (**Scheme 1.31**) (Ramsden and Rose, 1997) and hence it can perform

regioselective oxidations with a wide range of functional groups and in a variety of solvents, e.g. methanol, dichloromethane, acetonitrile and even water (Lou *et al.*, 2012), which is important for “green chemistry”. Another important feature of PIDA is its ability to be regenerated after the reaction (Ma *et al.*, 2012). This is especially important in industry where the reduction of waste has become an critical issue. PIDA has been used to perform various reactions in organic synthesis such as the Hofmann rearrangement, cyclization, halogenation and oxidation.

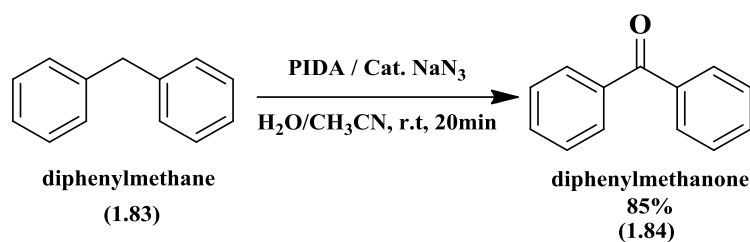


Scheme 1.31: Nucleophile exchange with PIDA

1.5.3 Phenyliodine(III) Diacetate Synthetic Utility: Oxidation

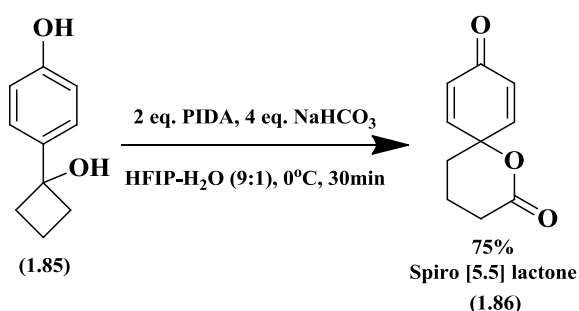
Hypervalent iodine compounds are capable of regioselective oxidation under mild conditions in the presence of a wide variety functional groups. PIDA has played a significant role in the syntheses of the heterocyclic moieties, which is a critical structural feature of a number of pharmacologically active compounds, e.g. quinoxaline (Aggarwal *et al.*, 2006), hydroxamic acid (Ghosh and Patel, 2010), sinomenine (Lou *et al.*, 2012).

Telvekar and Sasane (2012) applied the PIDA C-H oxidation to diphenylmethane (**1.83**) in acetonitrile/water at room temperature in the presence of catalytic amounts of sodium azide, to produce the diphenylmethanone (**1.84**) in 85% yield (**Scheme 1.42**).



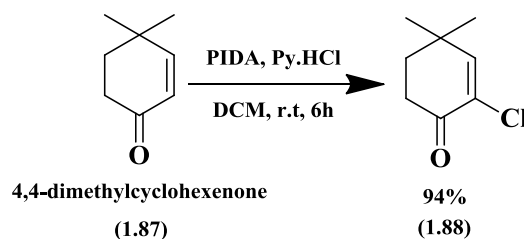
Scheme 1.32: Diphenylmethanone synthesis (Telvekar and Sasane, 2012)

PIDA not only can effect ring contractions, but also induce ring expansions through rearrangement. The spiro [5.5] lactone **1.86** was synthesized from 4-(1-hydroxycyclobutyl)phenol (**1.85**) via an oxidation-rearrangement promoted by PIDA with sodium bicarbonate as an additive in the presence of hexafluoroisopropanol (HFIP)/water in a ratio of 9:1 at 0°C (**Scheme 1.33**). It is believed that the water plays a vital role in this reaction (Fujioka *et al.*, 2010).

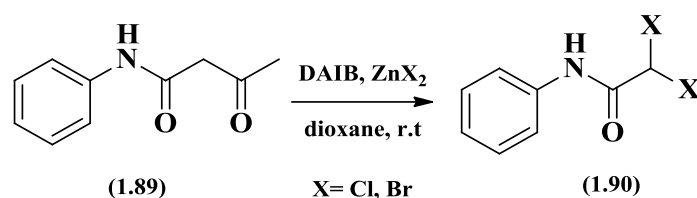


Scheme 1.33: Ring expansion reaction (Fujioka *et al.*, 2010)

As reported by Ngatimin *et al.* (2009), PIDA can act as a halogenation agent to give α -chlorination products (from enones) in good yields on various enones. Thus α -chlorination of 4,4-dimethylcyclohexenone (**1.87**) by means of PIDA in the presence of pyridine hydrochloride, yields the chlorinated cyclohexenone **1.88** (94%) (**Scheme 1.34**). In the presence of Lewis acids like ZnCl_2 or ZnBr_2 , Liu and co-workers (2012) effected the chlorination and bromination on the 3-oxo-*N*-phenylbutamide (**1.129**) where the Lewis acids serve as the halogen source (**Scheme 1.48**). The reaction can be applied to a number of substituted benzenes.

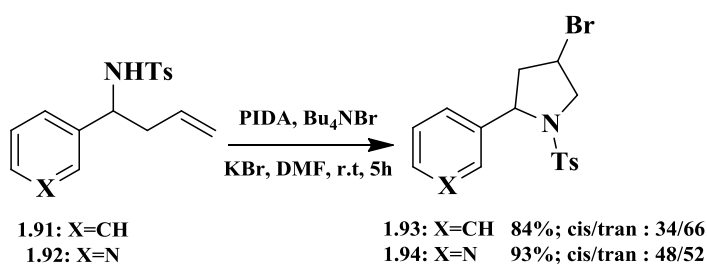


Scheme 1.34: Halogenation reaction (Ngatimin *et al.*, 2009)



Scheme 1.35: Liu's halogenation reaction (Liu *et al.*, 2012)

The spiro-annulation was achieved in 69% yield. 2-phenyl-4-bromo-pyrrolidine **1.93** was prepared by intramolecular oxidative bromocyclization of the **1.91** using the combination of PIDA, Bu₄NBr and KBr in DMF, to give the desired product **1.93** in 84% yield (**Scheme 1.36**), KBr in the reaction acts as the source of bromine (Fan *et al.*, 2007). Replacement of the benzene ring with pyridine **1.91** gave **1.94** even higher yields (93%) with a 48:52 = *cis/trans* ratio.

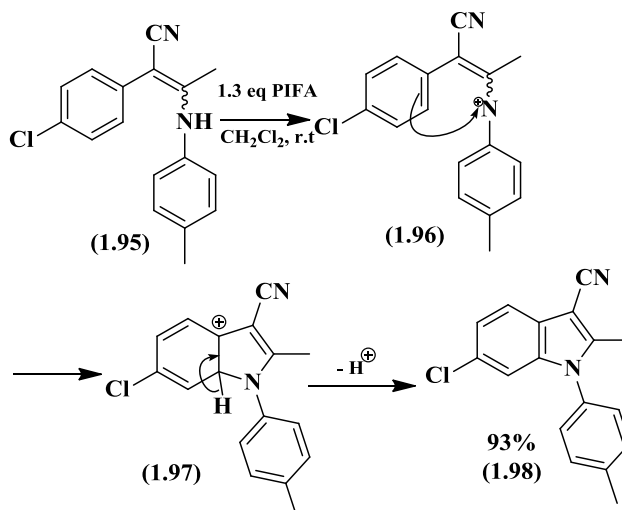


Scheme 1.36: Intramolecular oxidative bromocyclization (Fan *et al.*, 2007)

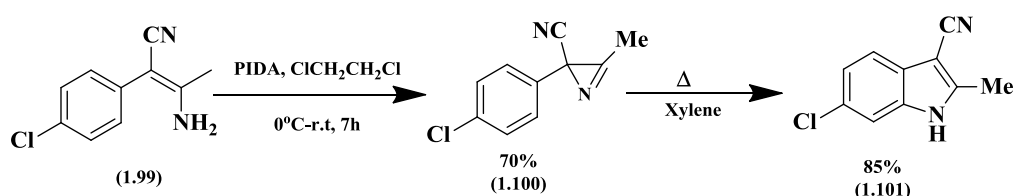
1.5.4 Hypervalent Iodine and Indole Synthesis

Since hypervalent iodine both selective in the reactions it promotes and environmentally friendly, it is the ideal reagent for the synthesis of indole/indoline derivatives. Zhao's group have employed both PIDA and PIFA for the synthesis of

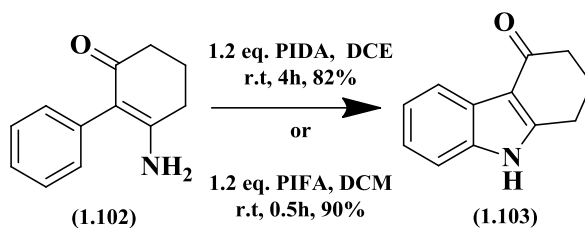
indoles. Du and co-workers (2006) first reported the synthesis of indole derivatives by PIFA-mediated intramolecular cyclization. The proposed mechanism is shown as in **Scheme 1.37**. The reaction involves the formation of the nitrenium ion followed by cyclization to the indole in 93% isolated yields. A few years later, Li's group (2009) reported in another paper the PIDA-promoted formation of azirines, which underwent thermal rearrangement to give the desired indole in 85% (**Scheme 1.38**). Recently, Ban reported that either PIDA or PIFA may be profitably exploited in the synthesis of the carbazolone from 2-aryl enaminones. The oxidative coupling reaction can be performed in different solvents, for example PIDA was used in dichloroethane while the reaction with PIFA was performed in dichloromethane. Either method gave excellent yields of the desired product (67-90%) (**Scheme 1.39**) (Ban *et al.*, 2012). Pouysegu *et al.* (2002) exploited a conjugate addition on a cyclohexadienone generated by mean of PIDA oxidation (**Scheme 1.40**).



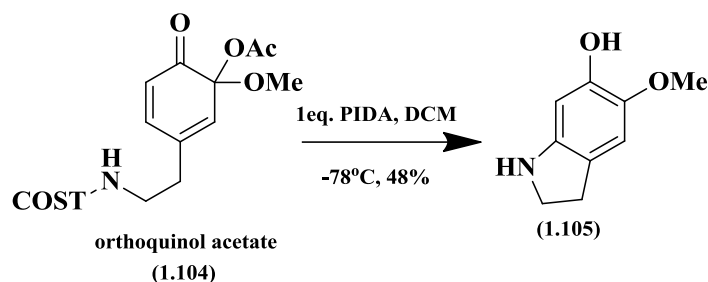
Scheme 1.37: PIFA-mediated intramolecular cyclization indole synthesis (Du *et al.*, 2006)



Scheme 1.38: Thermal rearrangement indole synthesis (Li *et al.*, 2009)

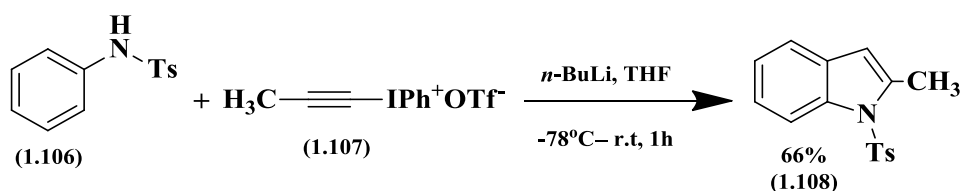


Scheme 1.39: Ban's PIDA or PIFA indole synthesis (Ban *et al.*, 2012)



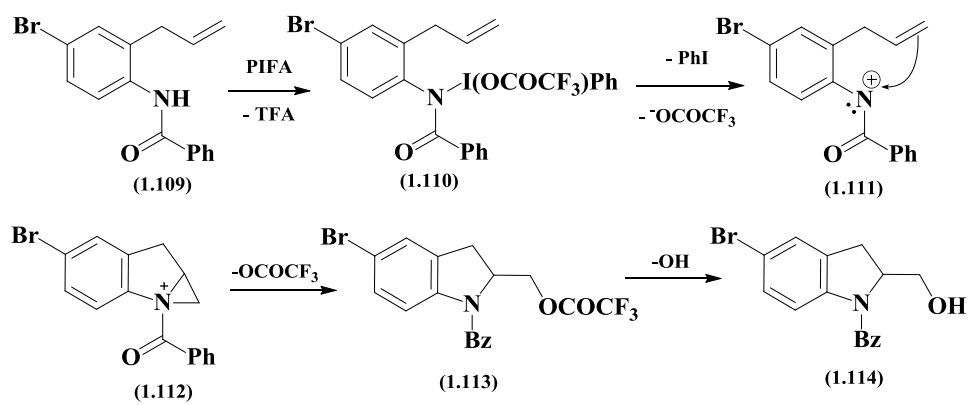
Scheme 1.40: Conjugate addition approach to indoline synthesis (Pouységu *et al.*, 2002)

Feldman *et al.* (1995) has shown that the indole ring can be prepared via the [3+2] cycloaddition of an anilide **1.106** with phenyl(propynyl)iodonium triflate (**1.107**) (Scheme 1.41). The mechanism of this transformation is not completely understood (Feldman *et al.*, 1995).



Scheme 1.41: [3+2] cycloaddition indole synthesis (Feldman *et al.*, 1995)

2-hydroxymethyl indoline (**1.114**) was synthesized by exposure of the 2-(allyl)anilide (**1.109**) to PIFA. The anilide nitrenium ion (**1.111**) which subsequently undergoes a 5-*exo-trig* cyclization to give **1.114** (Scheme 1.42) (Correa *et al.*, 2006).



Scheme 1.42: 2-hydroxymethyl indoline synthesis (Correa *et al.*, 2006)

Chapter 2

2.0 Experimental Section

2.1 General Remarks

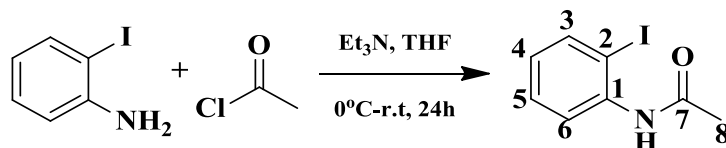
Unless otherwise noted, materials was purchased from commercial suppliers and used without purification. THF and DMF solvent were dried over molecular sieves 4Å (Merck) prior to use. Merck silica gel (0.040-0.063 mm) was used to perform column chromatography. Merck TLC aluminum sheets (silica gel 60 F₂₅₄) was used for thin layer chromatography. Nuclear magnetic resonance (NMR) spectra was obtained on Bruker Avance III 400 MHz, JEOL JNM-LA 400 and JEOL ECA-400. Spectra are reported in units of ppm on the scale, relative to chloroform and the coupling constants are given in Hz. Mass spectra were measured using Agilent 6530 Accurate-Mass Q-TOF LC/MS system. Melting points were determined with Mel-Temp II melting point apparatus.

2.2 General Procedure for the Preparation of

N-(2-iodophenyl)acylamides

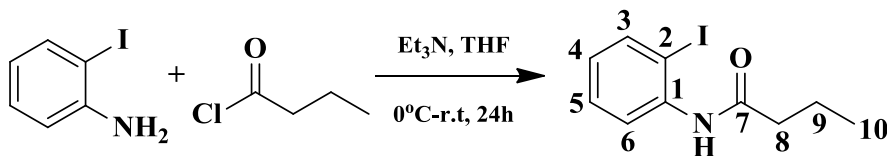
The acyl chloride (1 equiv.) in dry THF was added dropwise into a stirred, cooled solution of 2-iodoaniline (0-5°C) and Et₃N in dry THF. The ice bath was removed and the mixture was stirred vigorously at room temperature overnight. The solid Et₃N.HCl was filtered and washed with THF. The solvent was removed under reduced pressure and crude product purified by column chromatography to give the desired amide (Ladziata *et al.*, 2005).

2.2.1 *N*-(2-iodophenyl)acetamide (2.1)



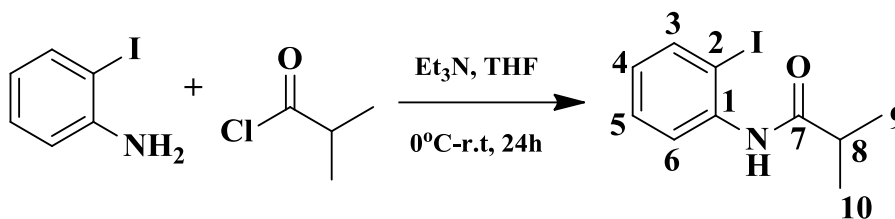
2-Iodoaniline (10.9512 g, 50 mmol) was treated with acetyl chloride (3.6 ml, 50.4 mmol) according to the general procedure. Recrystallization of the crude product from hexane/ CHCl_3 afforded an off-white solid. Yield 12.1440 g (93.7%). m.p. $106\text{--}107^\circ\text{C}$ [lit., $111\text{--}112^\circ\text{C}$ (Ahmad *et al.*, 2009)]. ^1H NMR (400 MHz, CDCl_3) δ = 8.17 (d, J = 7.6 Hz, 1H, H-6), 7.75 (d, J = 7.8 Hz, 1H, H-3), 7.40 (br s, 1H, NH), 7.32 (t, J = 7.3 Hz, 1H, H-4), 6.82 (t, J = 7.4 Hz, 1H, H-5), 2.22 (s, 3H, H-8, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ = 168.1 (C-7, $\text{C}=\text{O}$), 138.8 (C-3), 138.2 (C-1), 129.2 (C-4), 126.0 (C-5), 122.1 (C-6), 90.0 (C-2), 24.8 (C-8, CH_3).

2.2.2 *N*-(2-iodophenyl)butyramide (2.2)



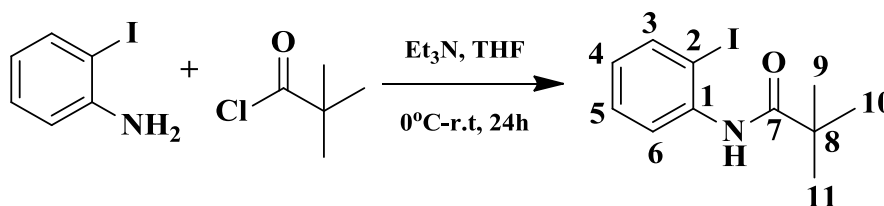
2-Iodoaniline (2.7459 g, 12.5 mmol) was treated with butyryl chloride (1.35 ml, 13.0 mmol) according to the general procedure. Recrystallization of the crude product from hexane/ CHCl_3 afforded an off-white solid. Yield 2.8122 g (77.6%). m.p. $81\text{--}83^\circ\text{C}$ [(lit., $83\text{--}84^\circ\text{C}$) (Kee *et al.*, 2010)]. ^1H NMR (400 MHz, CDCl_3) δ = 8.17 (d, J = 7.96 Hz, 1H, H-6), 7.75 (d, J = 6.72 Hz, 1H, H-3), 7.50 (br s, 1H, NH), 7.31 (t, J = 7.04 Hz, 1H, H-4), 6.82 (t, J = 7.36 Hz, 1H, H-5), 2.40 (t, J = 7.32 Hz, 2H, H-8), 1.78 (sextet, J = 7.80 Hz, 2H, H-9), 1.03 (t, J = 7.36 Hz, 3H, H-10). ^{13}C NMR (100 MHz, CDCl_3) δ = 171.3 (C-7, $\text{C}=\text{O}$), 138.8 (C-6), 129.4 (C-3), 126.0 (C-4), 122.1 (C-5), 90.0 (C-2), 40.0 (C-8, CH_2), 19.2 (C-9, CH_2), 13.7 (C-10, CH_3).

2.2.3 *N*-(2-iodophenyl)isobutyramide (2.3)



2-Iodoaniline (10.9506 g, 50.0 mmol) was treated with isobutyryl chloride (5.30 ml, 50.6 mmol) according to the general procedure. Recrystallization of the crude product from hexane/ CHCl_3 afforded an off-white solid. Yield 13.2299 g (91.5%). m.p. 110-111°C [lit., 117-118 °C (Kee *et al.*, 2010)]. ^1H NMR (400 MHz, CDCl_3) δ = 8.15 (d, J = 8.00 Hz, 1H, H-6), 7.68 (d, J = 7.92 Hz, 1H, H-3), 7.45 (br s, 1H, NH), 7.24 (t, J = 7.04 Hz, 1H, H-4), 6.74 (t, J = 7.64 Hz, 1H, H-5), 2.52 (septet, J = 6.88 Hz, 1H, H-8), 1.21 (dd, J = 1.84 Hz, J = 7.00 Hz, 6H, H-9, H-10, 2 x CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ = 175.3 (C-7, C=O), 138.8 (C-3), 138.2 (C-1), 129.4 (C-4), 125.9 (C-5), 122.0 (C-6), 90.2 (C-2), 37.2 (C-8, CH), 19.7 (C-9, C-10, 2x CH_3).

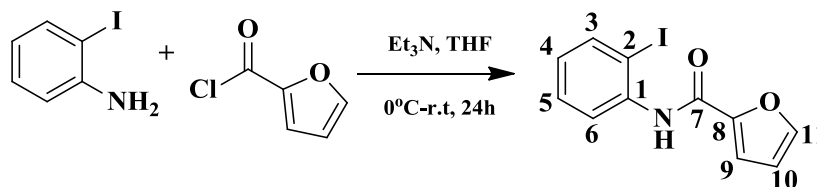
2.2.4 *N*-(2-iodophenyl)pivalamide (2.4)



2-Iodoaniline (10.9535 g, 50.0 mmol) was treated with pivaloyl chloride (6.20 ml, 50.4 mmol) according to the general procedure. Recrystallization of the crude product from hexane/ CHCl_3 afforded an off-white solid. Yield 13.5637 g (89.5%). m.p. 79-80°C [lit., 80-81°C]. ^1H NMR (400 MHz, CDCl_3) δ = 8.22 (dd, J = 8.2 Hz, J = 1.6 Hz, 1H, H-6), 7.79 (br s, 1H, NH), 7.69 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H, H-3), 7.28 (t, J = 7.6 Hz, 1H, H-4), 6.77 (td, J = 7.6 Hz, J = 1.6 Hz, 1H, H-5), 1.34 (s, 9H, H-9, H-10, H-11, 3 x CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ = 176.58 (C-7, C=O), 138.66 (C-3),

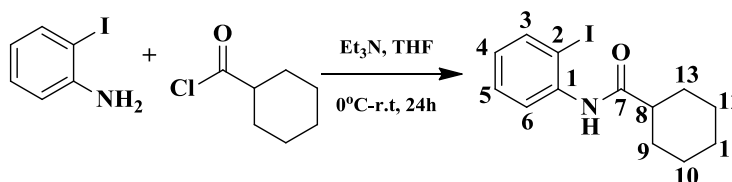
138.33 (C-1), 129.19 (C-4), 125.77 (C-5), 121.94 (C-6), 90.51 (C-2), 40.08 (C-8), 27.75 (C-9, C-10, C-11).

2.2.5 *N*-(2-iodophenyl)furan-2-carboxamide (2.5)



2-Iodoaniline (10.9522 g, 50.0 mmol) was treated with furoryl chloride (5.00 ml, 50.7 mmol) according to the general procedure. Recrystallization of the crude product from hexane/CHCl₃ afforded an off-white solid. Yield 12.0241 g (76.8%). m.p. 80-81°C. ¹H NMR (400 MHz, CDCl₃) δ = 8.54 (br s, 1H, NH), 8.39 (dd, J = 1.44 Hz, J = 8.16 Hz, 1H, H-6), 7.81 (dd, J = 1.24 Hz, J = 7.92 Hz, 1H, H-3), 7.58 (d, J = 1.68 Hz, 1H, H-11), 7.39 (td, J = 1.48 Hz, J = 7.84 Hz, 1H, H-5), 7.28 (d, J = 3.4 Hz, 1H, H-9), 6.88 (td, J = 1.48 Hz, J = 7.96 Hz, 1H, H-4), 6.59 (dd, J = 1.72 Hz, J = 3.68 Hz, 1H, H-10). ¹³C NMR (100 MHz, CDCl₃) δ = 156.1 (C-7, C=O), 147.7 (C-8), 144.8 (C-11), 139.0 (C-3), 138.0 (C-1), 129.4 (C-5), 126.1 (C-4), 121.7 (C-6), 115.8 (C-9), 112.8 (C-10), 89.9 (C-2).

2.2.6 *N*-(2-iodophenyl)cyclohexanecarboxamide (2.6)

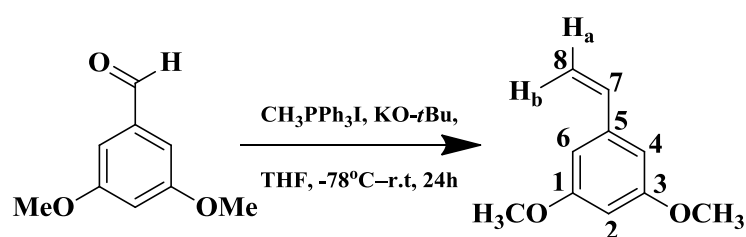


2-Iodoaniline (10.9526 g, 50.0 mmol) was treated with cyclohexane carbonyl chloride (6.70 ml, 50.1 mmol) according to the general procedure. Recrystallization of the crude product from hexane/CHCl₃ afforded an off-white solid. Yield 14.3978 g

(87.5%). m.p. 134-136°C [lit., 139-140°C (Kee *et al.*, 2010)]. ^1H NMR (400 MHz, CDCl_3) δ = 8.25 (d, J = 8.08 Hz, 1H, H-6), 7.76 (d, J = 8.08 Hz, 1H, H-3), 7.53 (br s, 1H, NH), 7.33 (t, J = 7.80 Hz, 1H, H-5), 6.83 (t, J = 7.56 Hz, 1H, H-4), 2.32 (tt, J = 3.4 Hz, J = 11.72 Hz, 1H, H-8), 1.24-2.06 (m, H-9, H-10, H-11, H-12, H-13, 10H, CH_2). ^{13}C NMR (100 MHz, CDCl_3) δ = 174.4 (C-7, C=O), 138.8 (C-3), 138.3 (C-1), 129.3 (C-5), 125.9 (C-4), 122.1 (C-6), 90.2 (C-2), 46.7 (C-8), 29.8 (C-9, 13, CH_2), 25.8 (C-10, 11, 13, CH_2).

2.3 Procedure for Preparation of 1,3-dimethoxy-5-vinylbenzene (2.7)

or Styrene



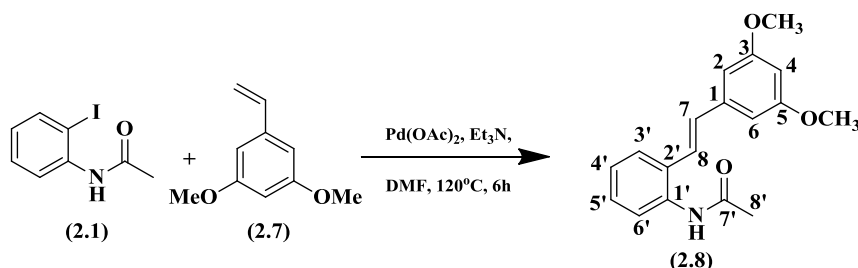
To a suspension of methyltriphenylphosphonium iodide (4.0667 g, 10.1 mmol) in dry THF, potassium *tert*-butoxide (1.5459 g, 13.8 mmol) was added in one portion. The mixture was stirred for 1 hour under nitrogen at -70°C to -80°C in dry ice. 3,5-Dimethoxy benzaldehyde (1.6776 g, 10.1 mmol) was added to the solution. The dry ice bath was removed and the mixture was allowed to warm to room temperature. After consumption of the benzaldehyde and product formation, the reaction was quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate and washed with distilled water (three times). The resulting organic extracts were combined and solvent was removed under reduced pressure to yield crude product. Purification by column chromatography afforded the 1,3-dimethoxy-5-vinylbenzene 1.2150 g (73.3%). ^1H NMR (400 MHz, CDCl_3) δ = 6.60 (dd, J = 17.6 Hz, J = 10.8 Hz, 1H, H-2), 6.53 (d, J = 2.4 Hz, 2H, H-4, H-6), 6.35 (t, J = 2.4 Hz, 1,

H-7), 5.67 (d, $J = 10.8$ Hz, 1H, H-8_b), 5.18 (d, $J = 17.6$ Hz, 1H, H-8_a), 3.70 (s, 6H, 2 x OCH₃). ¹³C NMR (100 MHz, CDCl₃) $\delta = 161.04$ (C-1, C-3), 139.66 (C-5), 137.01 (C-7), 114.19 (C-8, CH₂), 104.33 (C-4, C-6), 100.11 (C-2), 55.14 (2 x OCH₃). NMR shift values were in agreement with those of Ahmad *et al.* (2009).

2.4 General Procedure for the Preparation of Stilbenes

The *N*-(2-iodophenyl)acylamide **2.1-2.6** (1 equiv.) was dissolved in dry DMF in a dry, two neck flask and stirred under nitrogen. The solution was heated up to 120°C and refluxed for a few minutes. Palladium(II) acetate (1% mol) and triethylamine (5 equiv.) were added. 1,3-Dimethoxy-5-vinylbenzene (**2.7**) (1.2 equiv.) was added to the reaction flask. The mixture was refluxed under nitrogen for six hours. The reaction mixture was quenched with saturated ammonium chloride, extracted with ethyl acetate, and washed with distilled water. The resulting organic fractions were combined, dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to yield the crude product. Purification by column chromatography give the desired product.

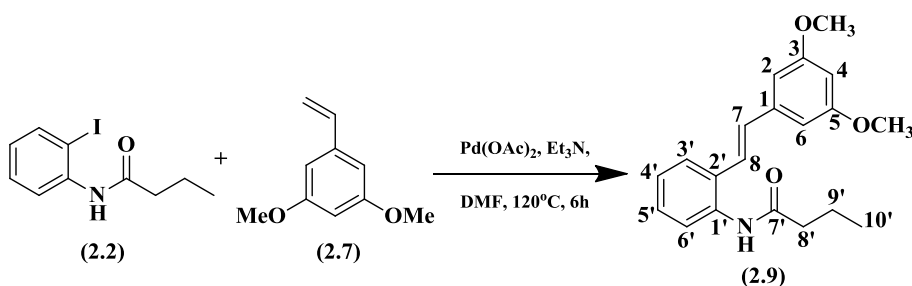
2.4.1 (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)acetamide (**2.8**)



N-(2-iodophenyl)acetamide **2.1** (0.5222 g, 2.00 mmol) was dissolved in 40 ml dry DMF. The solution was heated up to 120°C and refluxed under nitrogen for a few minutes. Palladium(II) acetate (6.0 mg, 0.027 mmol) was added to the reaction mixture,

followed by triethylamine (1.30 ml, 9.33 mmol). Styrene **2.7** (0.3962 g, 2.41 mmol) was added to the reaction mixture which was refluxed under nitrogen for six hours. The reaction mixture was worked up according to the general procedure. Purification of the crude product by column chromatography (hexane/ethyl acetate) afforded a white solid. Yield 0.3736 g (62.8 %). ^1H NMR (400 MHz, CDCl_3) δ = 7.73 (d, J = 8.0 Hz, 1H, H-6'). 7.49 (d, J = 7.6 Hz, 1H, H-3'), 7.39 (s, 1H, NH), 7.26 (t, J = 6.8 Hz, 1H, H-5'), 7.16 (t, J = 7.2 Hz, 1H, H-4'), 7.08 (d, J = 16.4 Hz, 1H, H-8), 6.86 (d, J = 16.0 Hz, 1H, H-7), 6.64 (t, J = 2.0 Hz, 2H, H-2, H-6), 6.42 (d, J = 2.0 Hz, 1H, H-4), 3.81 (s, 6H, 2 x OMe), 2.18 (s, 3H, H-8'). ^{13}C NMR (100 MHz, CDCl_3) δ = 168.82 (C-7', C=O), 161.04 (C-3, C-5), 139.07 (C-1), 134.69 (C-1'), 132.24 (C-7), 130.34 (C-2'), 128.39 (C-5'), 126.82 (C-3'), 125.66 (C-4'), 124.51 (C-6'), 124.14 (C-8), 104.93 (C-2, C-6), 100.04 (C-4), 55.42 (2 x OCH_3), 24.22 (C-8'), NMR shift values were in agreement with those of Ahmad *et al.* (2009).

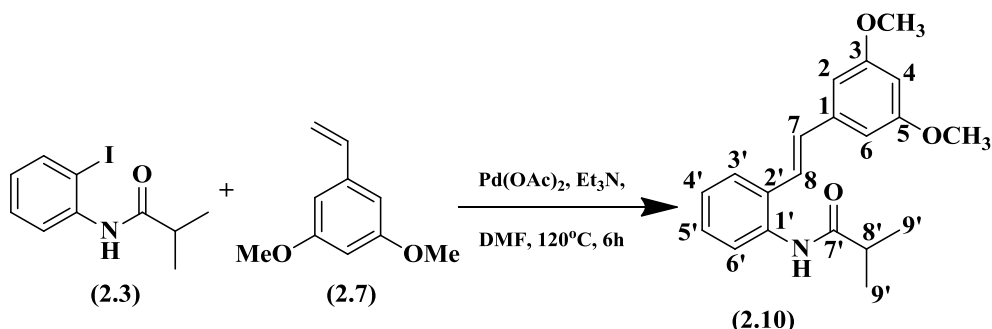
2.4.2 (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)butyramide (**2.9**)



N-(2-iodophenyl)butyramide **2.2** (0.5790 g, 2.00 mmol) was dissolved in 40 ml dry DMF. The solution was heated up to 120°C and refluxed under nitrogen for a few minutes. Palladium(II) acetate (5.4 mg, 0.024 mmol) was added to the reaction mixture, followed by triethylamine (1.30 ml, 9.33 mmol). Styrene **2.7** (0.4015 g, 2.45 mmol) was added to the reaction mixture which was refluxed under nitrogen for six hours. The reaction mixture was worked up according to the general procedure. Purification of the crude product by column chromatography (hexane/ethyl acetate) afforded a

white solid. Yield 0.4025 g (61.76%). ^1H NMR (400 MHz, CDCl_3) δ = 7.68 (d, J = 7.2 Hz, H-6'), 7.48 (d, J = 6.4 Hz, 1H, H-3'), 7.21 (t, J = 6.8 Hz, 1H, H-5'), 7.13 (t, J = 6.8 Hz, 2H, H-4', NH overlap), 7.08 (d, J = 16.0 Hz, 1H, H-8), 6.85 (d, J = 16.0 Hz, 1H, H-7), 6.61 (d, J = 2.0 Hz, 2H, H-2, H-6), 6.40 (t, J = 2.0 Hz, 1H, H-4), 3.79 (s, 6H, 2 x OCH_3), 2.32 (t, J = 6.8 Hz, 2H, H-8'), 1.74 (m, J = 7.2 Hz, 2H, H-9'), 0.99 (t, J = 7.2 Hz, 3H, H-10'). ^{13}C NMR (100 MHz, CDCl_3) δ = 171.08 (C-7', C=O), 161.03 (C-3, C-5), 139.10 (C-1), 134.74 (C-1'), 131.85 (C-7), 130.51 (C-2'), 128.29 (C-5'), 126.65 (C-3'), 125.58 (C-4'), 124.75 (C-6'), 124.15 (C-8), 104.82 (C-2, C-6), 100.13 (C-4), 55.36 (2 x OCH_3), 39.28 (C-8'), 19.31 (C-9'), 13.82 (C-10'). HRMS (+ESI) $[\text{M}+\text{H}]^+$: 326.1756, $\text{C}_{20}\text{H}_{24}\text{NO}_3$ requires 326.1756.

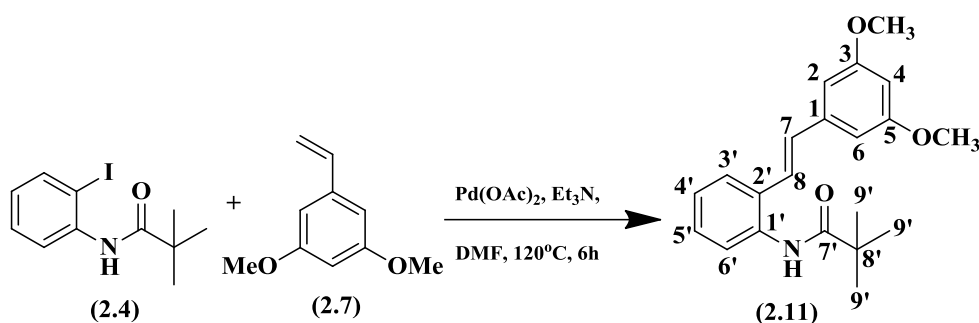
2.4.3 (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)isobutyramide (2.10)



N-(2-iodophenyl)isobutyramide **2.3** (0.5782 g, 2.00 mmol) was dissolved in 40 ml dry DMF. The solution was heated up to 120°C and refluxed under nitrogen for a few minutes. Palladium(II) acetate (5.6 mg, 0.025 mmol) was added to the reaction mixture, followed by triethylamine (1.30 ml, 9.33 mmol). Styrene **2.7** (0.3991 g, 2.43 mmol) was added to the reaction mixture which was refluxed under nitrogen for six hours. The reaction mixture was worked up according to the general procedure. Purification of the crude product by column chromatography (hexane/ethyl acetate) afforded a white solid. Yield 0.3825 g (58.78%). ^1H NMR (400 MHz, CDCl_3) δ = 7.83 (d, J = 7.6 Hz, 1H, H-6'), 7.51 (d, J = 7.2 Hz, 1H, H-3'), 7.28 (td, J = 7.7 Hz, 1H, H-5'), 7.18 (m,

2H, H-4', NH overlap), 7.10 (d, $J = 16.0$ Hz, 1H, H-8), 6.92 (d, $J = 16.0$ Hz, 1H, H-7), 6.64 (d, $J = 2.4$ Hz, 2H, H-2, H-6), 6.43 (t, $J = 2.2$ Hz, 1H, H-4), 3.82 (s, 6H, 2 x OCH₃), 2.58 (m, 1H, H-8'), 1.29 (d, $J = 6.8$ Hz, 6H, H-9', 2 x CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 175.26 (C-7', C=O), 161.09 (C-3, C-5), 139.00 (C-1), 134.75 (C-1'), 132.53 (C-7), 130.16 (C-1'), 128.45 (C-3'), 126.99 (C-5'), 125.44 (C-4'), 124.12 (C-6'), 124.04 (C-8), 104.78 (C-2, C-6), 100.26 (C-4), 55.39 (2 x OCH₃), 36.52 (C-8'), 19.72 (C-9', 2 x CH₃). HRMS (+ESI) [M+H]⁺: 326.1781, C₂₀H₂₄NO₃ requires 326.1756.

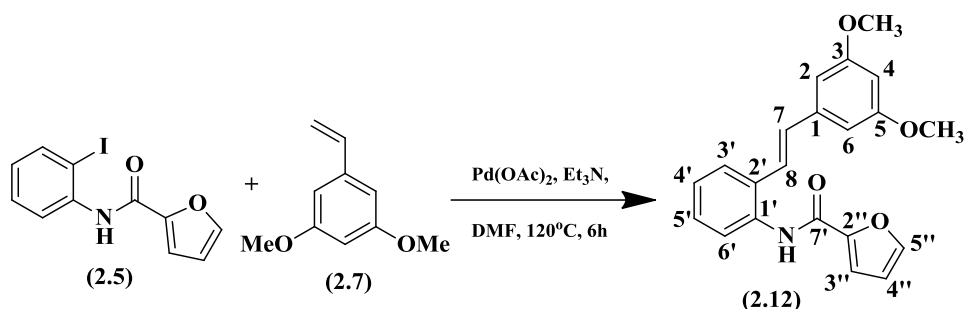
2.4.4 (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)pivalamide (**2.11**)



N-(2-iodophenyl)pivalamide **2.4** (0.6071 g, 2.00 mmol) was dissolved in 40 ml dry DMF. The solution was heated up to 120°C and refluxed under nitrogen for a few minutes. Palladium(II) acetate (5.0 mg, 0.022 mmol) was added to the reaction mixture, followed by triethylamine (1.30 ml, 9.33 mmol). Styrene **2.7** (0.3986 g, 2.43 mmol) was added to the reaction mixture which was refluxed under nitrogen for six hours. The reaction mixture was worked up according to the general procedure. Purification of the crude product by column chromatography (hexane/ethyl acetate) afforded a white solid. Yield 0.4605 g (67.74%). ¹H NMR (400 MHz, CDCl₃) δ = 7.69 (d, $J = 7.20$ Hz, 1H, H-3'), 7.53 (br s, NH), 7.48 (d, $J = 7.60$ Hz, 1H, H-6'), 7.22 (m, 1H, H-4'), 7.14 (t, $J = 7.60$ Hz, 1H, H-5'), 7.05 (d, $J = 16.00$ Hz, 1H, H-8), 6.86 (d, $J = 16.00$ Hz, 1H, H-7), 6.60 (d, $J = 2.00$ Hz, 2H, H-2, H-6), 6.40 (t, $J = 2.20$ Hz, 1H, H-4), 3.78

(s, 6H, 2 x OCH₃), 1.31 (s, 9H, H-9', 3 x CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 176.75 (C-7', C=O), 161.09 (C-3, C-5), 139.05 (C-1), 134.95 (C-2'), 132.13 (C-7), 130.74 (C-1'), 128.29 (C-4'), 126.79 (C-6'), 125.52 (C-5'), 124.63 (C-3'), 124.01 (C-8), 104.65 (C-2, C-6), 100.32 (C-8), 55.31 (2 x OCH₃), 39.62 (C-8'), 27.69 (C-9', 3 x CH₃). HRMS (+ESI) [M+H]⁺ : 340.1909, C₂₁H₂₆NO₃ requires 340.1913.

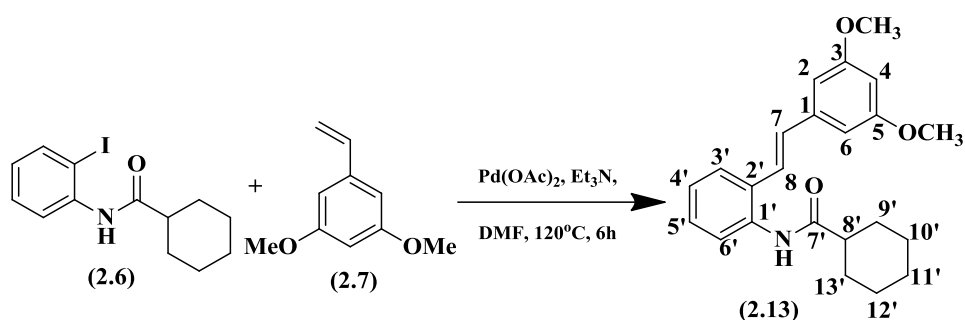
2.4.5 (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)furan-2-carboxamide (**2.12**)



N-(2-iodophenyl)furan-2-carboxamide **2.5** (0.6273 g, 2.00 mmol) was dissolved in 40 ml dry DMF. The solution was heated up to 120°C and refluxed under nitrogen for a few minutes. Palladium(II) acetate (6.0 mg, 0.027 mmol) was added to the reaction mixture, followed by triethylamine (1.30 ml, 9.33 mmol). Styrene **2.7** (0.3949 g, 2.40 mmol) was added to the reaction mixture which was refluxed under nitrogen for six hours. The reaction mixture was worked up according to the general procedure. Purification of the crude product by column chromatography (hexane/ethyl acetate) afforded a white solid. Yield 0.4520 g (64.57%). ¹H NMR (400 MHz, CDCl₃) δ = 8.19 (br s, 1H, NH), 7.98 (d, *J* = 8.4 Hz, 1H, H-6'), 7.51 (dd, *J* = 7.6 Hz, 1H, H-3'), 7.47 (d, *J* = 1.6 Hz, 1H, H-5''), 7.30 (td, *J* = 7.6 Hz, *J* = 14.0 Hz, 1H, H-5'), 7.20 (d, *J* = 5.2 Hz, 1H, H-4'), 7.16 (d, *J* = 8.4 Hz, 1H, H-3''), 7.15 (d, *J* = 16.0 Hz, 1H, H-8), 6.92 (d, *J* = 16.0 Hz, 1H, H-7), 6.64 (d, *J* = 2.0 Hz, 2H, H-2, H-6), 6.53 (dd, *J* = 1.6 Hz, 1H, H-4''), 6.41 (t, *J* = 2.4 Hz, 1H, H-4), 3.78 (s, 6H, 2 x OCH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 161.06 (C-3, C-5), 156.31 (C-7', C=O), 147.90 (C-2''), 144.43 (C-5''),

139.06 (C-1), 134.18 (C-1'), 132.81 (C-7), 130.00 (C-2'), 128.48 (C-5'), 127.19 (C-3'), 125.55 (C-4'), 123.86 (C-8), 123.68 (C-6'), 115.40 (C-3''), 112.60 (C-4''), 104.92 (C-2, C-6), 100.22 (C-4), 55.38 (2 x OCH₃). NMR shift values were in agreement with those of Kee *et al.* (2010).

2.4.6 (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)cyclohexanecarboxamide (2.13)

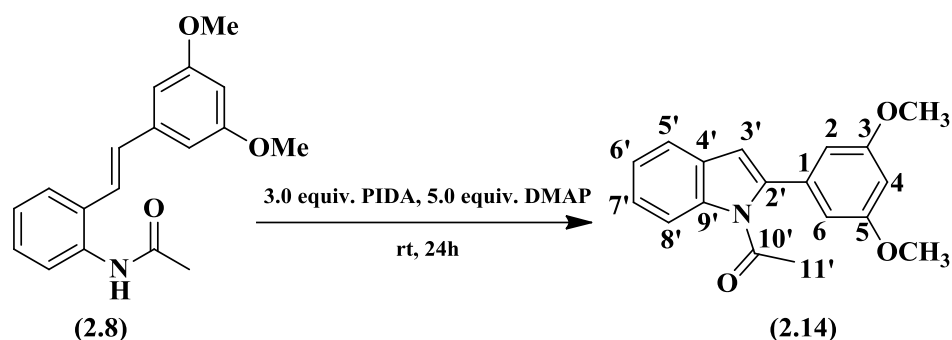


N-(2-iodophenyl)cyclohexanecarboxamide **2.6** (0.6586 g, 2.00 mmol) was dissolved in 40 ml dry DMF. The solution was heated up to 120°C and refluxed under nitrogen for a few minutes. Palladium(II) acetate (6.3 mg, 0.028 mmol) was added to the reaction mixture, followed by triethylamine (1.30 ml, 9.33 mmol). Styrene **2.7** (0.3989 g, 2.43 mmol) was added to the reaction mixture which was refluxed under nitrogen for six hours. The reaction mixture was worked up according to the general procedure. Purification of the crude product by column chromatography (hexane/ethyl acetate) afforded a white solid. Yield 0.4376g (59.84%). ¹H NMR (400 MHz, CDCl₃) δ = 7.77 (d, *J* = 8.0 Hz, 1H, H-6'), 7.51 (d, *J* = 7.6 Hz, 1H, H-3'), 7.25-7.29 (m, 2H, H-5', NH overlap), 7.16 (t, *J* = 7.6 Hz, 1H, H-4'), 7.09 (d, *J* = 16.4 Hz, 1H, H-8), 6.90 (d, *J* = 16.0 Hz, 1H, H-7), 6.64 (d, *J* = 2.4 Hz, 2H, H-2, H-6), 6.42 (t, *J* = 2.4 Hz, 1H, H-4), 3.82 (s, 6H, 2 x OCH₃), 2.30 (tt, *J* = 11.6 Hz, *J* = 3.2 Hz 1H, H-8'), 1.22-2.01 (m, 10H, H-9', H-10', H-11', H-12', H-13') ¹³C NMR (100 MHz, CDCl₃) δ = 174.53 (C-7', C=O), 161.04 (C-3, C-5), 139.06 (C-1), 134.75 (C-1'), 132.25 (C-7), 130.33 (C-2'), 128.41 (C-5'), 126.86 (C-3'), 125.49 (C-4'), 124.39 (C-6'), 124.09 (C-8), 104.73

(C-2, C-6), 100.23 (C-4), 55.37 (2 x OCH₃), 46.19 (C-8'), 29.83 (C-9', C-13'), 25.69 (C-10', C-12'), 25.66 (C-11'). HRMS (+ESI) [M+H]⁺ : 366.1333, C₂₃H₂₈NO₃ requires 366.2069.

2.5 Preparation of 1-(2-(3,5-dimethoxyphenyl)-1H-indol-1-yl)ethanone

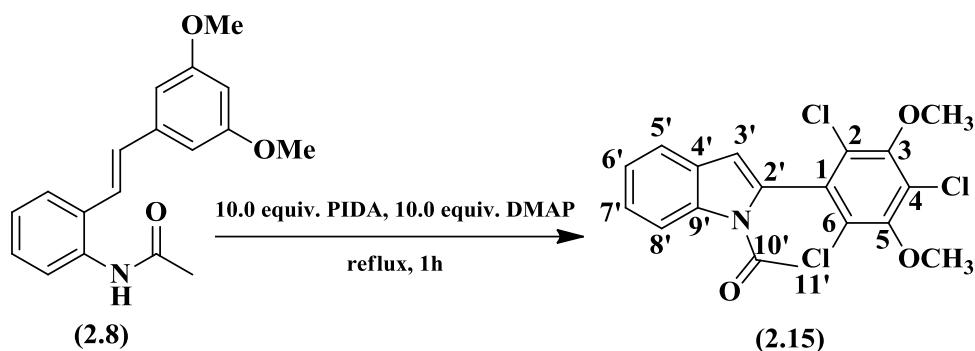
(2.14)



To a stirred solution of (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)acetamide (**2.8**) (0.1232 g, 0.41 mmol) dissolved in 30 mL DCM, 2,4-dimethyl aminopyridine (DMAP) (0.2444 g, 2.00 mmol) and phenyliodine diacetate (PIDA) (0.3870 g, 1.20 mmol) was added into the mixture. The solution was stirred for 24 hours at room temperature. The reaction mixture was quenched with saturated ammonium chloride and extracted with DCM and washed with distilled water. The resulting organic fraction were combined, dried over anhydrous sodium sulphate and solvent was removed under reduced pressure to yield the crude product. Purification by column chromatography gave the product **2.14** 0.0098 g (8.28%). ¹H NMR (400 MHz, CDCl₃) δ = 8.36 (dd, *J* = 1.2 Hz, *J* = 8.2 Hz, 1H, H-8'), 7.55 (dq, *J* = 0.4 Hz, *J* = 7.6 Hz, 1H, H-5'), 7.36 (td, *J* = 1.6 Hz, *J* = 7.6 Hz, 1H, H-7'), 7.28 (ddd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H, H-6'), 6.64 (s, 1H, H-3'), 6.62 (d, *J* = 2.4 Hz, 2H, H-2, H-6), 6.52 (t, *J* = 2.4 Hz, 1H, H-4), 3.83 (s, 6H, 2 x OCH₃), 2.18 (s, 3H, H-11', CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 171.57 (C-10', C=O), 160.97 (C-3, C-5), 139.56 (C-1), 137.69 (C-2'), 135.96 (C-9'), 128.89 (C-4'), 125.18 (C-7'), 123.69 (C-6'), 120.41 (C-5'), 115.98 (C-8'), 111.39 (C-3'), 107.22 (C-

2, C-6), 100.60 (C-4), 55.51 (2 x OCH₃), 27.56 (C-11'). HRMS (+ESI) [M+H]⁺ : 296.1285, C₁₈H₁₈NO₃ requires 296.1287.

2.6 Preparation of 1-(2-(2,4,6-trichloro-3,5-dimethoxyphenyl)-1H-indol-1-yl)ethanone (2.15)



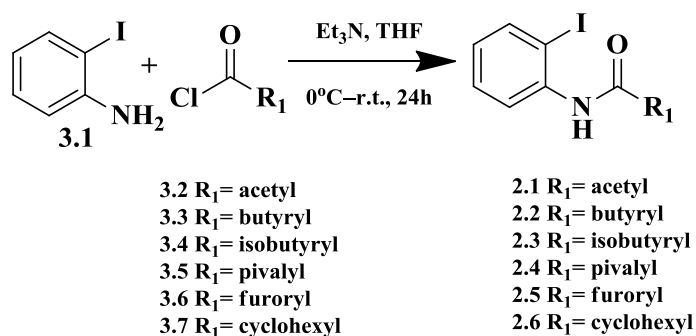
To a stirred solution of (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)acetamide (**2.8**) (0.1190 g, 0.40 mmol) dissolved in 30 mL DCM, 2,4-dimethyl aminopyridine (DMAP) (0.4895 g, 4.01 mmol) and phenyliodine diacetate (PIDA) (1.2891 g, 4.00 mmol) was added into it. The solution was refluxed for 1 hour. The reaction mixture was quenched with saturated ammonium chloride and extracted with DCM and washed with distilled water. The resulting organic fraction were combined, dried over anhydrous sodium sulphate and solvent was removed under reduced pressure to yield the crude product. Purification by column chromatography gave the product **2.15** 0.0092 g (5.77%). ¹H NMR (400 MHz, CDCl₃) δ = 8.49 (d, *J* = 8.4 Hz, 1H, H-8'), 7.65 (d, *J* = 7.6 Hz, 1H, H-5'), 7.46 (td, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H, H-7'), 7.39 (t, *J* = 7.6 Hz, 1H, H-6'), 6.72 (s, 1H, H-3'), 4.00 (s, 6H, 2 x OCH₃), 2.16 (s, 3H, H-11', CH₃). ¹³C NMR (100 MHz, CDCl₃) δ = 169.11 (C-10', C=O), 154.88 (C-3, C-5), 135.50 (C-1), 132.08 (C-2'), 128.93 (C-9'), 127.03 (C-4'), 126.72 (C-7'), 124.14 (C-6'), 118.56 (C-5'), 117.08 (C-8'), 116.04 (C-4), 115.55 (C-2, C-6), 98.37 (C-3'), 56.60 (2 x OCH₃), 25.27 (C-11'). HRMS (+ESI) [M+H]⁺ : 398.0118, C₁₈H₁₅Cl₃NO₃ requires 398.0118.

Chapter 3

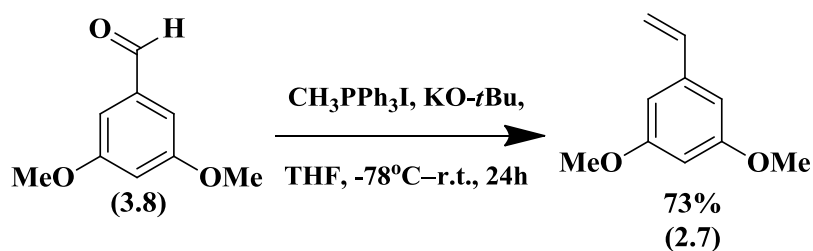
3.0 Results and discussion

3.1 Synthesis of Starting Material for Stilbenes

A total of six iodophenylamides **2.1-2.6** were prepared by reacting iodoaniline with the corresponding acyl chloride according to **Scheme 3.1** according to the procedure of Ladziata *et al.* (2005). The products were recrystallized from hexane/ CHCl_3 to produce the anilides **2.1** to **2.6** in yields varying from 77% to 93%. The 1,3-dimethoxy-5-vinylbenzene (**2.7**) was synthesized by the Wittig reaction. This 3,5-dimethoxy benzaldehyde was transformed to the corresponding styrene by treatment with methyltriphenylphosphonium iodide and potassium *tert*-butoxide in dry THF to give the product in 73% yield after silica gel chromatography as shown in **Scheme 3.2**.

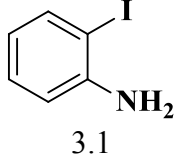
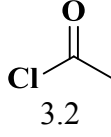
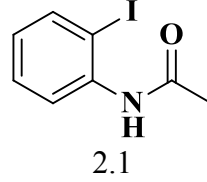
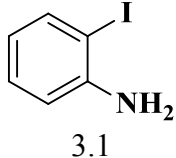
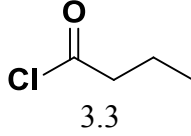
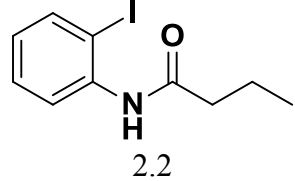
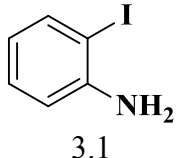
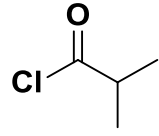
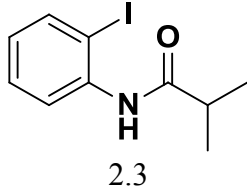
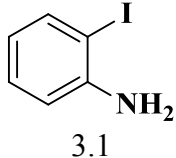
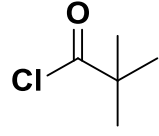
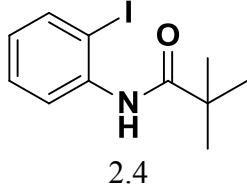
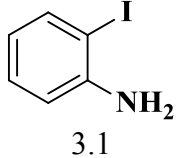
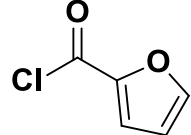
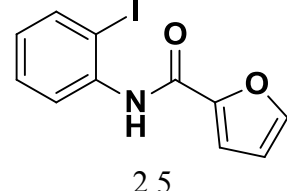
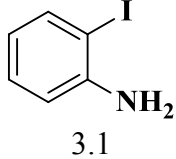
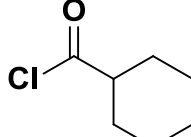
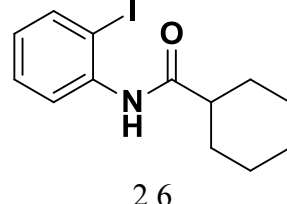


Scheme 3.1: The preparation of *N*-(2-iodophenyl)acylamides

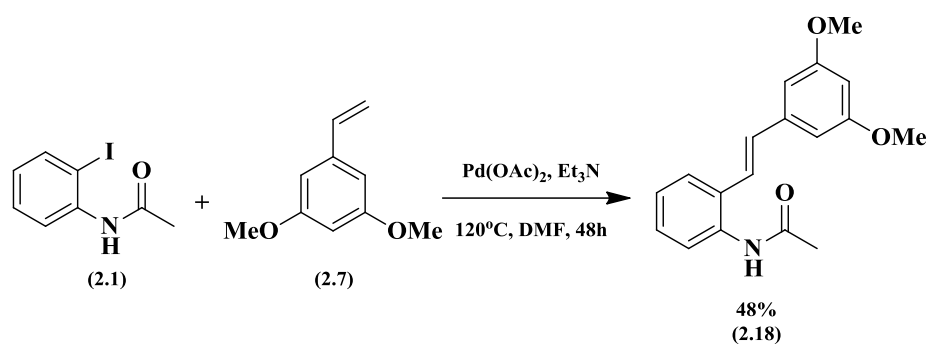


Scheme 3.2: Preparation of styrene via the Wittig reaction

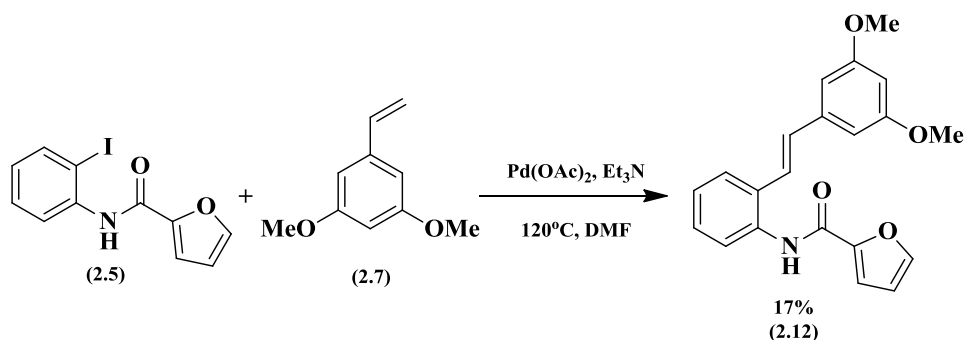
Table 3.1: Preparation of *N*-(2-iodophenyl)acylamides

Entry	SM 1	SM 2	Protected Amide	Yield (%)
1	 3.1	 3.2	 2.1	93.7
2	 3.1	 3.3	 2.2	77.6
3	 3.1	 3.4	 2.3	91.5
4	 3.1	 3.5	 2.4	89.5
5	 3.1	 3.6	 2.5	76.8
6	 3.1	 3.7	 2.6	87.5

Various factors can affect the yield of reaction, such as reaction time, temperature, catalyst, solvent and base. As previously reported by our group, Kartini *et. al.* performed the Heck reaction on *N*-(2-iodophenyl)acetamide **2.1** with 48 hours refluxed to give (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)acetamide **2.8** in 48%. Later Kee *et. al.* reported that reaction time was decided by monitoring the reaction until starting material was consumed, this method gave low yield to the stilbenes especially for (*E*)-*N*-(2-(3,5-dimethoxystyryl)phenyl)furan-2-carboxamide **2.12** where only 17% obtained. The long reaction times using by Kartini *et. al.* could lead to stilbene decomposition. Longer reaction times will lead to more by products.



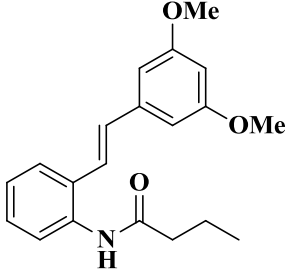
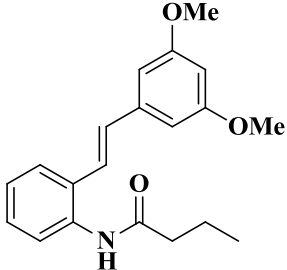
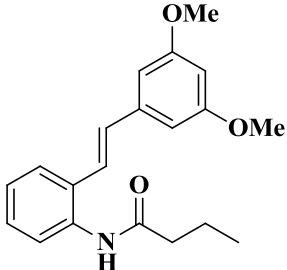
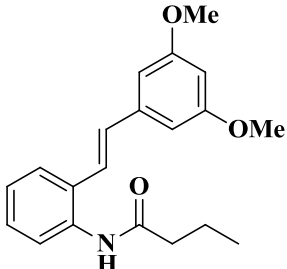
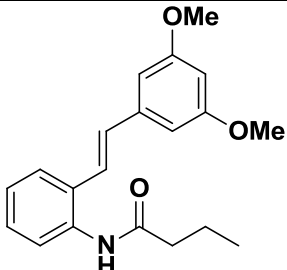
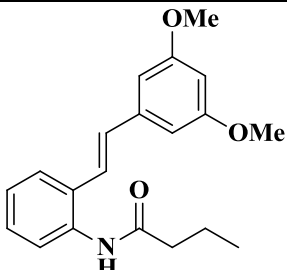
Scheme 3.3: Kartini *et. al.*'s Heck reaction

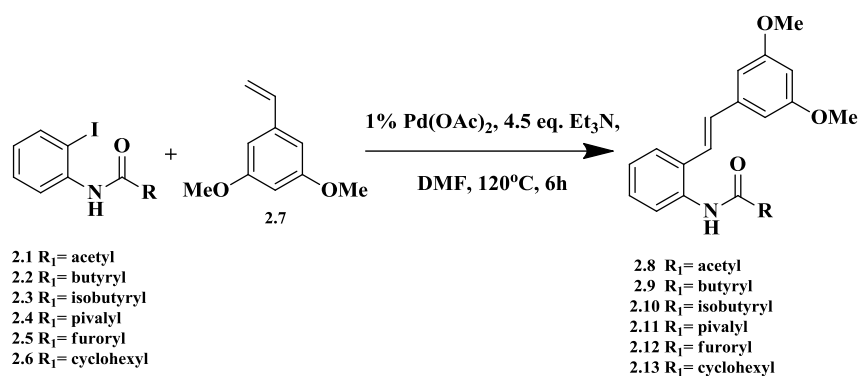


Scheme 3.4: Kee *et. al.*'s Heck reaction

N-(2-iodophenyl)butyramide **2.2** was exposed to styrene (**2.7**) in the presence of Pd(OAc)₂ and the reaction time was set as the variable with of reducing the reaction time lower than 12 hours, while other variables were held constant. The result of the reaction time optimization is summarized in **Table 3.2**. The yield of reaction increase from 49.76% to 61.76% when the reaction time increase from three to six hours and dropped from 57.97% and 56.34% when the reaction time was seven and eight hour respectively. From this we can conclude that the optimum reaction time for the stilbene synthesis was six hours. Longer reaction times may result in decomposition.

Table 3.2: Yield of stilbenes with different reaction times

Entry	Stilbene	Reaction Time (h)	Yields (%)
1		3	49.76
2		4	50.41
3		5	53.64
4		6	61.76
5		7	57.97
6		8	56.34

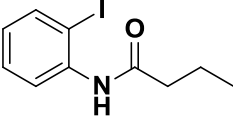
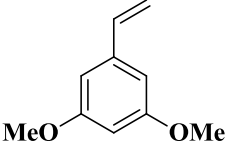
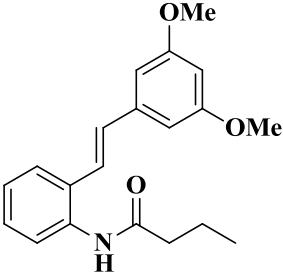
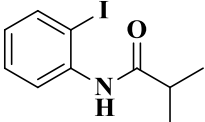
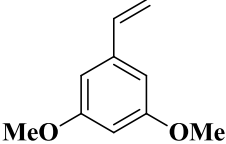
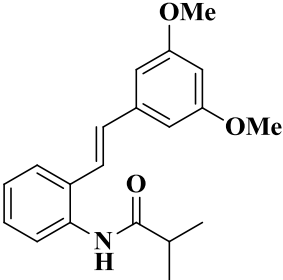
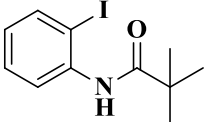
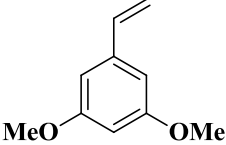
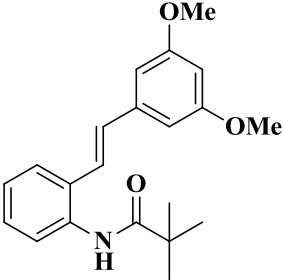
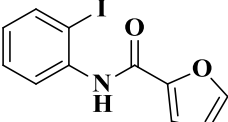
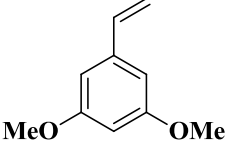
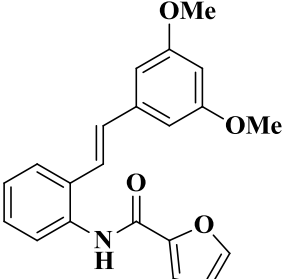
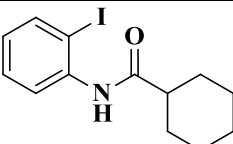
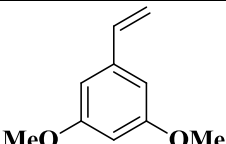
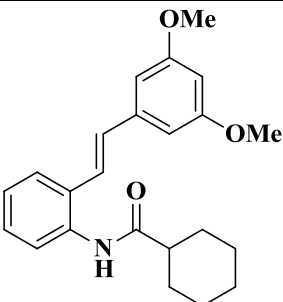


Scheme 3.5: Optimized condition for the Heck reaction

With the building blocks **2.1** to **2.7** in hand, the stage was set for the improved Heck reaction (**Scheme 3.5**) as shown in **Table 3.3**. By means of an improved procedure, the yield of the stilbene derivatives (**2.8** to **2.13**) varied from 58% to 68%. With the **Entry 4 (Table 3.3)** the pivaloylamidostilbene **2.11** gave the highest yield. In the case of **Entry 1** and **Entry 5** where previous reported yields were 45% and 17% respectively, yields following the improved procedure are 62.8% and 64.6%. Acetamidostilbene **2.8** in contrast to the previously reported conditions in **Scheme 3.3** (reaction time of 48 hours, 4 mol% of Et₃N base, 2% mol Pd(OAc)₂) (Ahmad *et al.*, 2009). The yield for furancarboxamidostilbene (**2.12**) (**Entry 5, Table 3.3**) was higher than that reported in **Scheme 3.4** by Kee *et al.* (2010). We discovered that shorter reaction times of six hours were possible with 4.5 equivalent Et₃N base led to an improved yield.

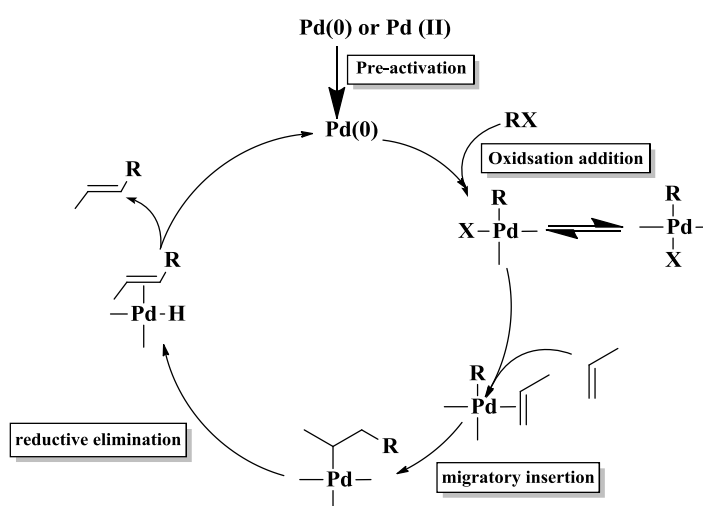
Table 3.3: Stilbenes derivatives synthesized via the Heck reaction

Entry	SM 1	SM 2	Stilbenes	Yield (%)
1	 2.1	 2.7	 2.8	62.8

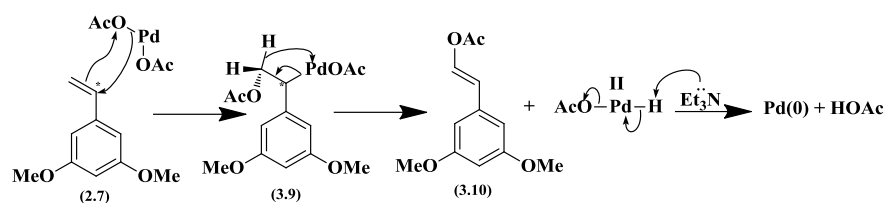
2	 2.2	 2.7	 2.9	61.8
3	 2.3	 2.7	 2.10	58.8
4	 2.4	 2.7	 2.11	67.7
5	 2.5	 2.7	 2.12	64.6
6	 2.6	 2.7	 2.13	59.8

3.1.1 Mechanistic Interpretation of Results for the Heck Reaction

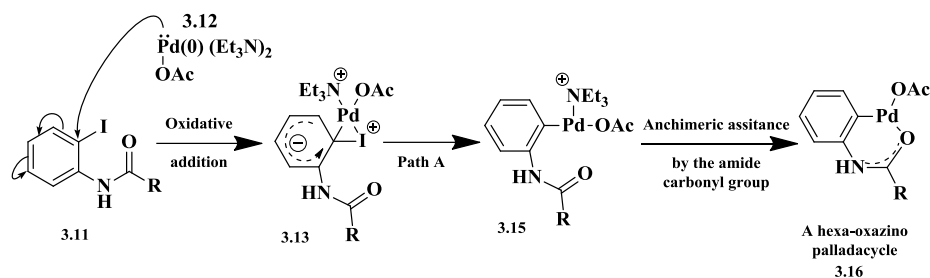
The reaction mechanism for the Heck reactions leading to orthocarboxamidostilbenes is more complex than the simplified Heck reaction scheme shown below (**Scheme 3.6**). The reaction starts with the activation of the palladium catalyst by reduction of Pd(II) to Pd(0) by styrene **2.7** (**Scheme 3.7**). Triethylamine also can be an effectively reducer for Pd(II) to Pd(0). The next step in the Heck reaction is the oxidative addition. The activated palladium catalyst is proposed to be in the form of **3.12** which was first suggested by Knowles and Whiting (2007) (**Scheme 3.8**). This proposal would be particularly relevant for the furancarboxamide group which is more electron-withdrawing compared to the acetamido group. This intermediate **3.13** is subsequently transformed to the hexa-oxazino palladacycle (**3.16**) as proposed by Horino and Inoue (1981). The hexa-oxazino palladacycle **3.16** is now set up for the styrene insertion (**Scheme 3.9**). The styrene is incorporated into **3.16** to yield the expanded palladacycle **3.17**. This undergoes base-promoted fragmentation to produce the stilbene. Pd(0), the active catalyst, is regenerated in this step.



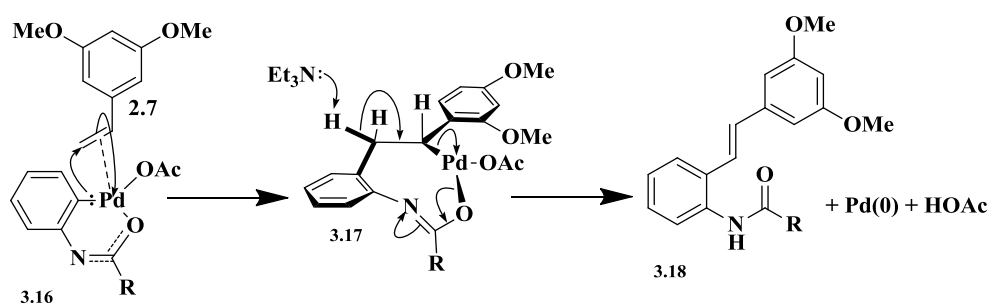
Scheme 3.6: A general mechanism for the Heck reaction



Scheme 3.7: Reduction of Pd(II) to Pd(0) by styrene

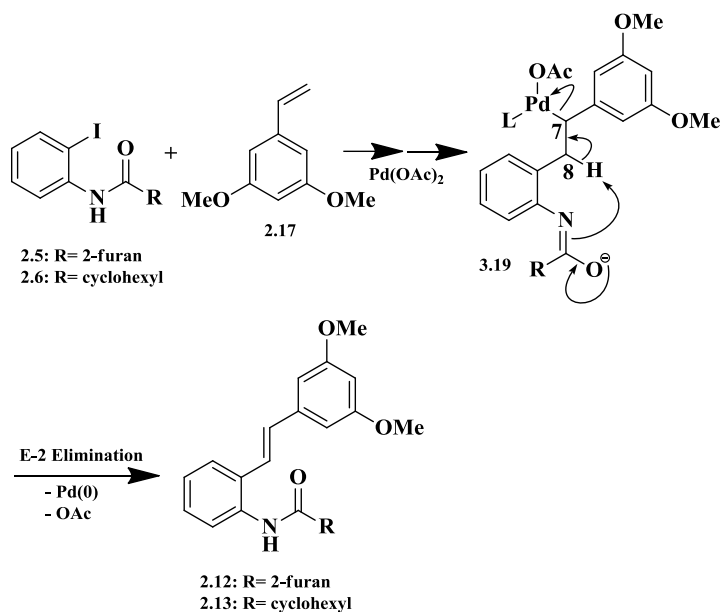


Scheme 3.8: Proposed oxidative addition step (Horino and Inoue, 1981; Knowles and Whiting, 2007)



Scheme 3.9: Styrene insertion into the palladacycle **3.16**

In an alternative pathway **3.19**, a non-cyclic palladium intermediate undergoes E-2 elimination via removal of the C-8 proton by the “internal base” (**Scheme 3.10**). This pathway may be the more favoured when R is large e.g. cyclohexyl.



Scheme 3.10: E-2 elimination via the “internal” base

3.2 Indole Synthesis

As report previously, indole (Page 1, **Scheme 1.3**) and indoline (Page 2, **Scheme 1.2**) was synthesized from stilbene using manganese triacetate ($\text{Mn}(\text{OAc})_3$) and iron (III) chloride (FeCl_3) respectively, the oxidative cyclization promoted by these two oxidizing reagents was discussed in detail in Thomas *et al.* 2004. In an effort to find suitable oxidizing agent which can give higher yields the formation of indole/indoline, agents were examined, such as ammonium cerium(IV) nitrate (CAN), sodium periodate (NaIO_4), silver permanganate (AgMnO_4), copper(II) bromide (CuBr_2), phenyliodine diacetate (PIDA), phenyliodine bis(trifluoroacetate) (PIFA). By using methanol as solvent, after stirring for 24 hours at room temperature (and monitor by TLC), only PIDA gave positive (**Figure 3.1**). the TLC indicated four major spots.

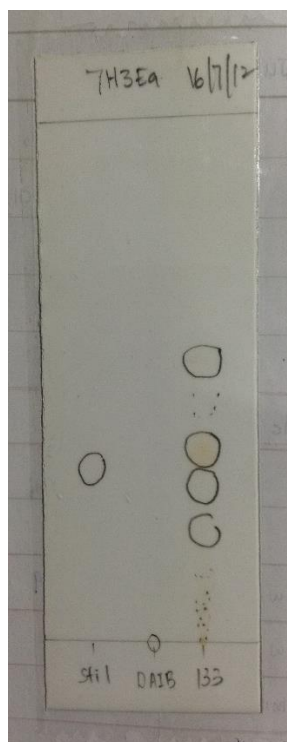
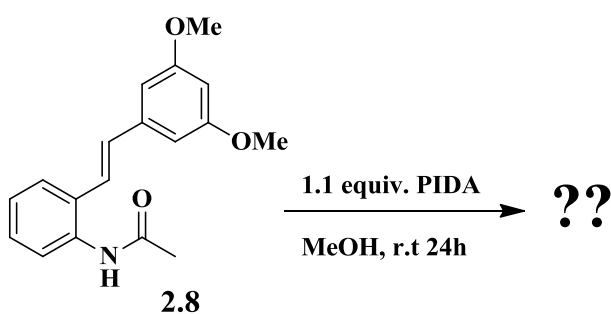


Figure 3.1: TLC for stilbene reaction with PIDA in methanol



Scheme 3.11: Stilbene oxidation with PIDA

The PIDA reaction as shown in **Scheme 3.11** was extract with ethyl acetate and purified by flash and radial chromatography. Unfortunately the major products visible by TLC, could not be isolated. The various solvents, base and temperature used are summarised in **Table 3.4**.

Table 3.4: Various reaction conditions tested for indole synthesis.

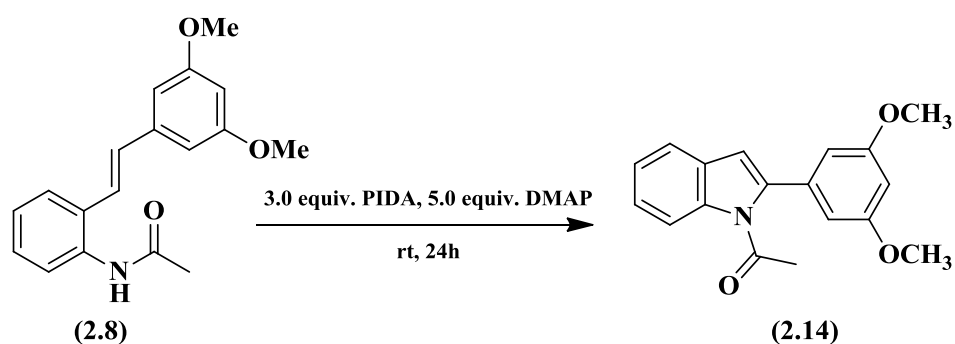
Entry	PIDA (equiv.)	Base	Solvent	Temperature/Time	Indole 2.14 yield (%)
1	1	-	MeOH	r.t, 24h	No product isolated
2	1	1 equiv. DMAP	MeOH	r.t, 24h	No product isolated
3	1	1 equiv. DMAP	Acetonitrile	r.t, 24h	No Reaction
4	1	2 equiv. DMAP	Acetonitrile	r.t, 24h	No Reaction
5	1	1 equiv. DMAP	DCM	r.t, 24h	4.0
6	1.2	2.5 equiv. DMAP	DCM	Reflux, 4h	5.6
7	3	5 equiv. DMAP	DCM	Reflux, 1h	4.2
8	3	5 equiv. DMAP	DCM	Reflux, 4h	6.9
9	3	5 equiv. DMAP	DCM	r.t, 24h	8.3
10	10	10 equiv. DMAP	DCM	Reflux, 1h	5.8*
11	10	10 equiv. DMAP	DCM	Reflux, 3h	5.1*
12	3	5 equiv. Et ₃ N	DCM	r.t, 24h	No Reaction
13	3	5 equiv. Et ₃ N	DCM	Reflux, 4h	No Reaction

*rt = room temperature

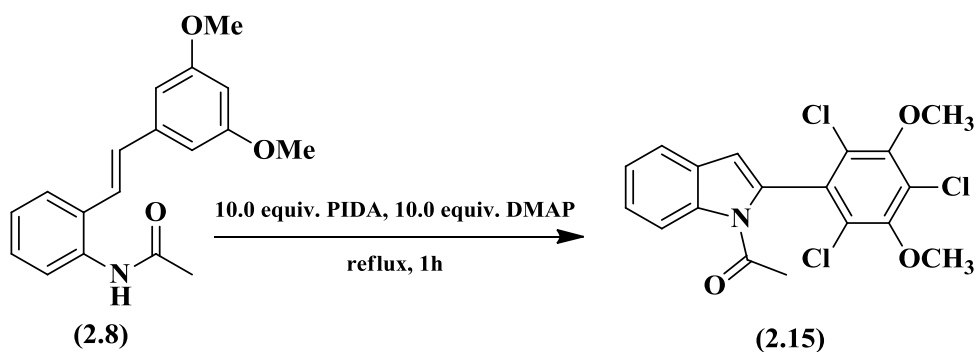
^a = trichloro indole (2.15**) obtained

No reaction was observed when acetonitrile was used as solvent even when the ratio of DMAP to PIDA was increased to 2:1 (**Table 3.4, Entry 3 and 4**). When the solvent was changed to dichloromethane (DCM) and in the presence of 1 equivalent of DMAP base, the indole was obtained in 4% yield (**Entry 5**). Changing the ratio of PIDA to DMAP with reflux for 4 hours increased the yield marginally from 4% to 5.6% (**Entry 6**), and the further slight increase resulting from a both the ratio of PIDA to DMAP (3:5) (**Entry 8**). A marginal increase in yield was obtained when the reaction

was stirred for 24 hours in CH_2Cl_2 at room temperature compared to reflux temperature (compare entry 9 with entries 6 to 8). For entries 10 and 11, when 10 equivalent of PIDA and DMAP added, a trichloroindole **2.15** was obtained. It is believed the chlorine incorporated into indole **2.15** could have originated from dichloromethane. The change from DMAP to Et_3N produced nothing of significance whether at room or reflux temperatures (**Entry 12** and **13**). After few attempts, the best reaction condition where as depicted in **Entry 9** (shown in Scheme 3.12) and as of trichloroindole is **Entry 10** (shown in Scheme 3.13).



Scheme 3.12: PIDA oxidative cyclization indole **2.14** synthesis

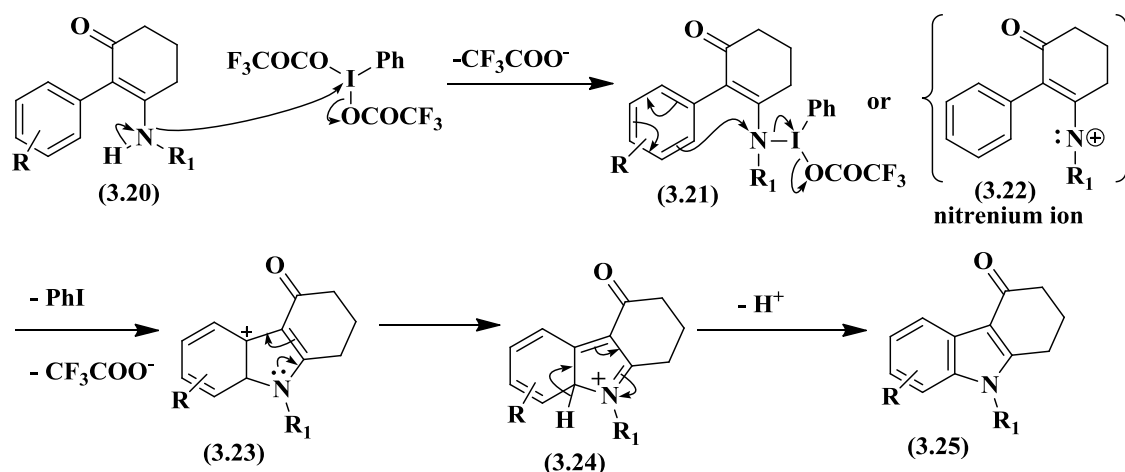


Scheme 3.13: PIDA oxidative cyclization trichloroindole **2.15** synthesis

3.2.1 Mechanistic Interpretation of Results for the PIDA Oxidative

Cyclization

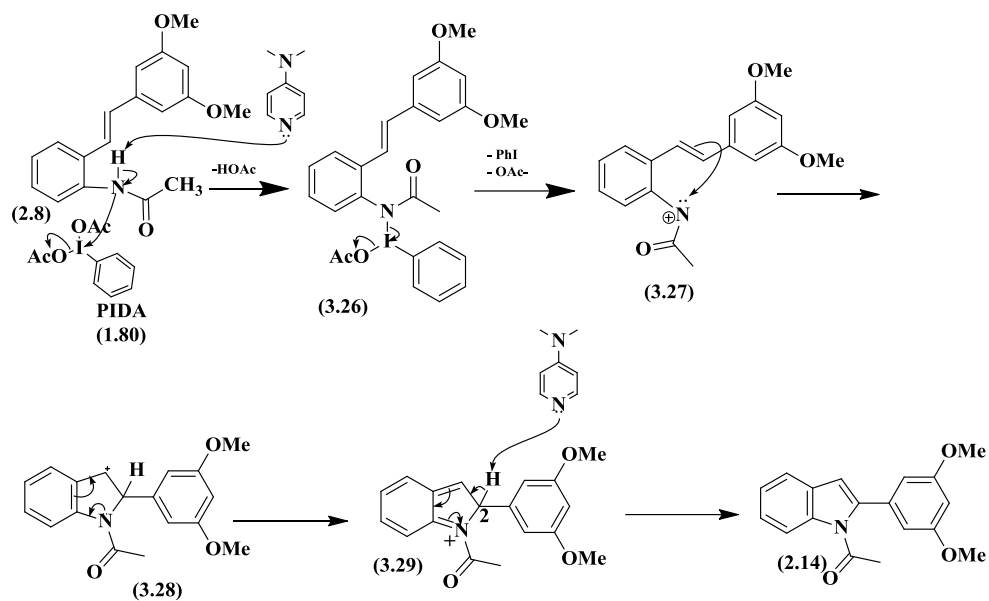
Year 2012, Ban *et al.* reported the PIFA oxidative cyclization route to indole derivatives and proposed the following mechanism for their reaction as shown in **Scheme 3.14**.



Scheme 3.14: Ban *et al.* proposed PIFA oxidative cyclization mechanism (Ban *et al.*, 2012)

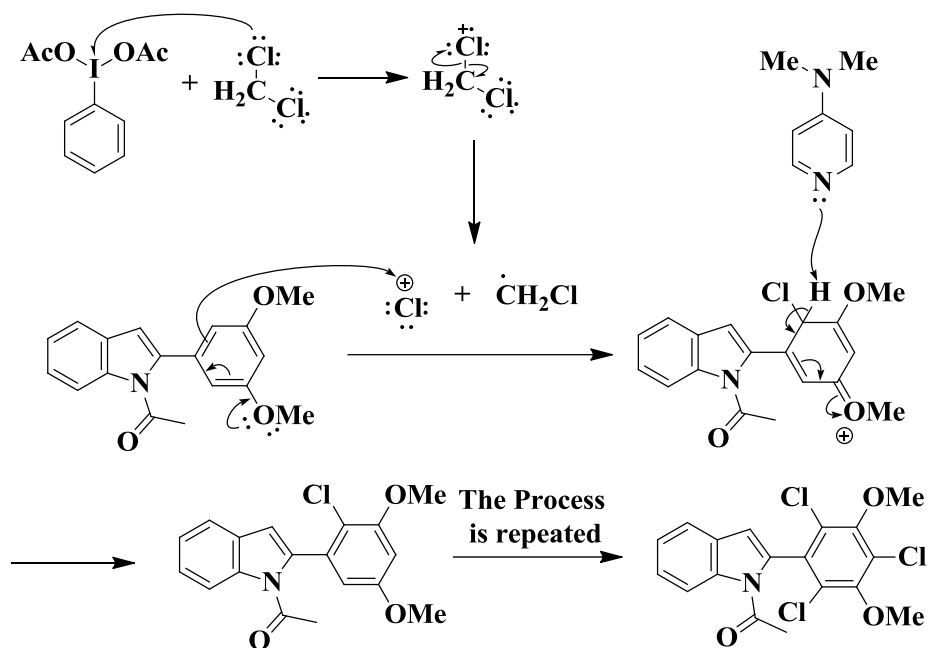
The above Ban mechanism implies attack by the benzene ring on an electron deficient N (with loss of PhI and CF_3COO^-) **3.21** (or attack on the nitrenium ion **3.22**). Based on this hypothesis, we suggest that treatment of our stilbene **2.8**, **Scheme 3.15** with PIDA should generate the nitrenium ion which is set up for nucleophilic attack by the stilbene double bond leading to the indole **2.14**.

The low yield of the indole could be attributed to side reactions e.g. polymerisation brought about by oxidation of the stilbene olefin to the radical cation leading to polar products that were difficult to isolate by chromatographic means.

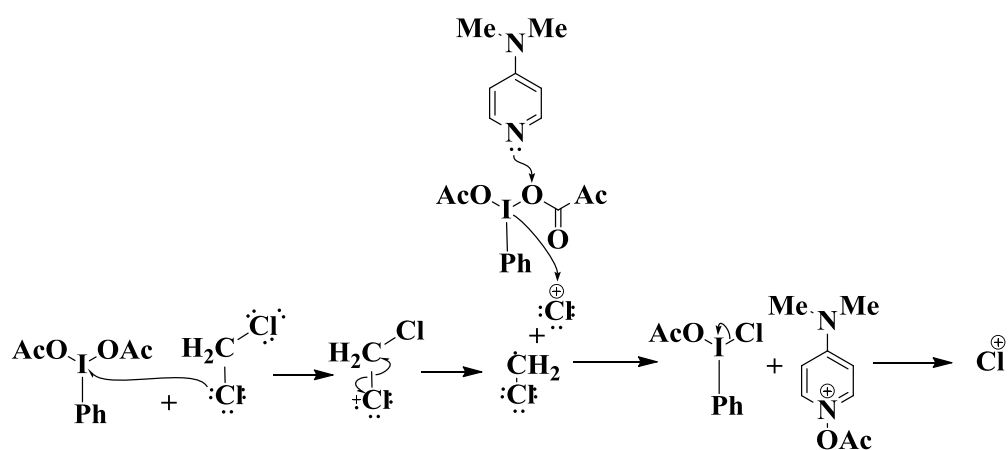


Scheme 3.15: Possible mechanism for PIDA-mediated cyclization

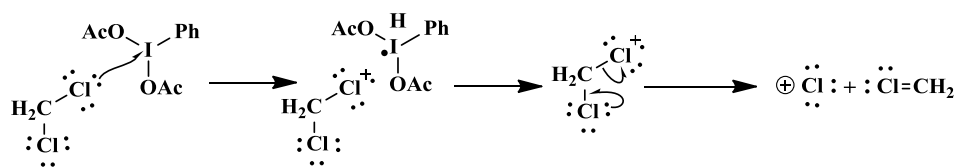
For the formation of trichloroindole, radical cation mediated decomposition of CH_2Cl_2 released Cl^\oplus . The electrophilic chlorination of the indole formed is depicted in **Scheme 3.16**. Two possible mechanism for the generation of Cl^\oplus are presented: DMAP mediated transformation of PIDA to the chloro derivative resulting from uptake of Cl^\oplus (**Scheme 3.17**). Alternatively, the decomposition of the CH_2Cl_2 is promoted by PIDA without DMAP involvement (**Scheme 3.18**).



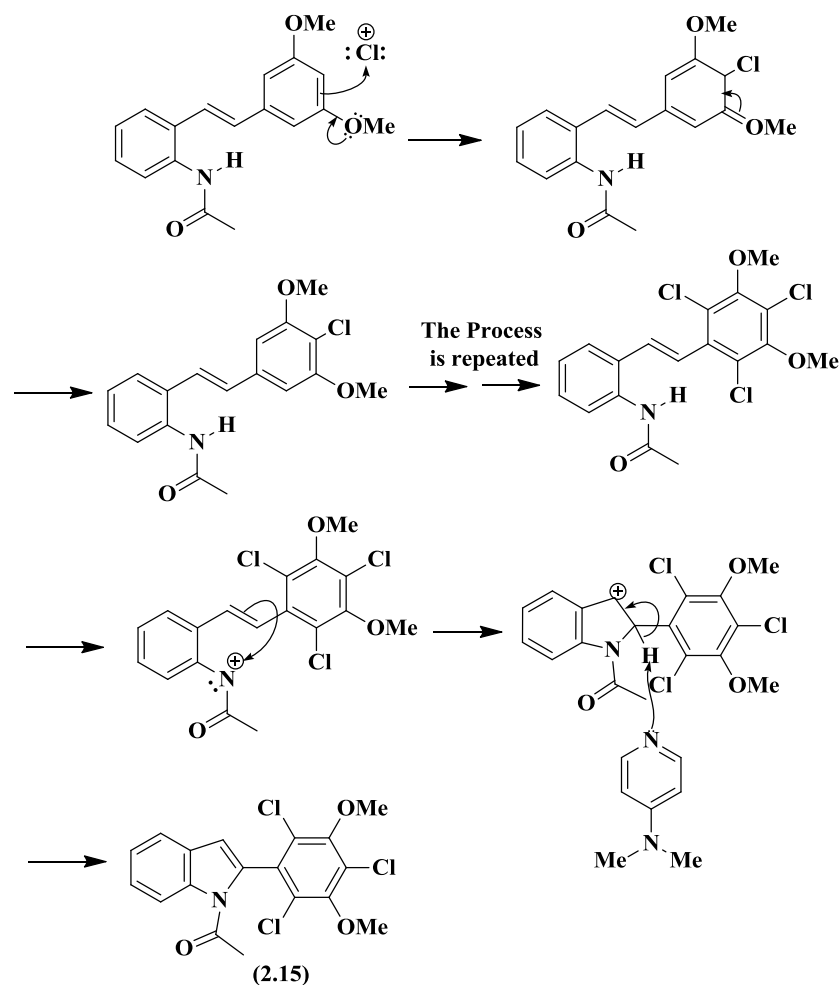
Scheme 3.16: First proposed trichloroindole formation mechanism



Scheme 3.17: First hypothesis for generation of Cl^+



Scheme 3.18: An alternative hypothesis for Cl^+ generation



Scheme 3.19: Second possible proposed trichloro stilbene cyclization

Comparison of the ^1H -NMR of both indole **2.14** and trichloro-indole **2.15** is shown in **Figure 3.1**. It is noteworthy that the C-10, C-12 and C-14 carbon are significantly more shield in **2.15** as these carbons bear chloro substituents as can be observed by comparing the chemical shifts of these carbons with the corresponding carbons in **2.14** (see **Table 3.5**). HRMS confirmed that the chlorine molecules appear in the indole **2.15** with $[\text{M}+\text{H}]^+$ shown 398.0118 (requiring 398.0118), while $[\text{M}+\text{H}]^+$ for indole **2.14** is 296.1285 (requiring 296.1287).

Table 3.5: ^1H NMR [400 MHz, δ_{H} (J, Hz)] and ^{13}C NMR [100 Hz, δ_{C}] in CDCl_3

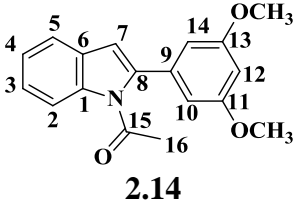
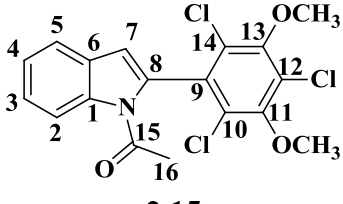
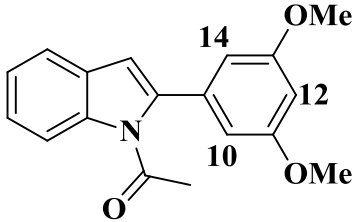
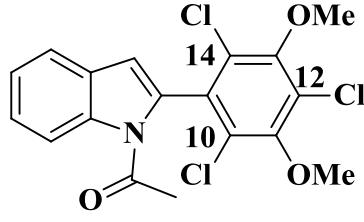
No.	 2.14		 2.15	
	^1H (J Hz)	^{13}C	^1H	^{13}C
1	-	135.96	-	128.93
2	8.35 (dd, 1.2, 8.2)	115.98	8.49 (d, 8.4)	117.08
3	7.36 (td, 1.6, 7.6)	125.18	7.46 (td, 1.2, 7.2)	126.72
4	7.28 (dq, 0.7, 7.6)	123.69	7.39 (t, 7.6)	124.14
5	7.55 (dq, 0.7, 7.6)	120.41	7.65 (d, 8.4)	118.56
6	-	128.89	-	127.03
7	6.64 (s)	111.39	6.72 (s)	98.37
8	-	137.69	-	132.08
9	-	139.56	-	135.50
10/14	6.62 (d, 2.4)	107.22	-	115.55
11/13	-	160.97	-	154.88
12	6.52 (t, 2.4)	100.60	-	116.04
11/13 -OMe	3.83 (s)	55.51	4.00 (s)	56.60
15	-	171.57	-	169.11
16	2.18 (s)	27.56	2.16 (s)	25.27

Table 3.6: Comparison on HRMS

 <p>2.14</p>		 <p>2.15</p>	
[M+H] ⁺	296.1285 (Required: 296.1287)	[M+H] ⁺	398.0118 (Required: 398.0118)
Molecular formula	C ₁₈ H ₁₈ NO ₃	Molecular formula	C ₁₈ H ₁₅ Cl ₃ NO ₃

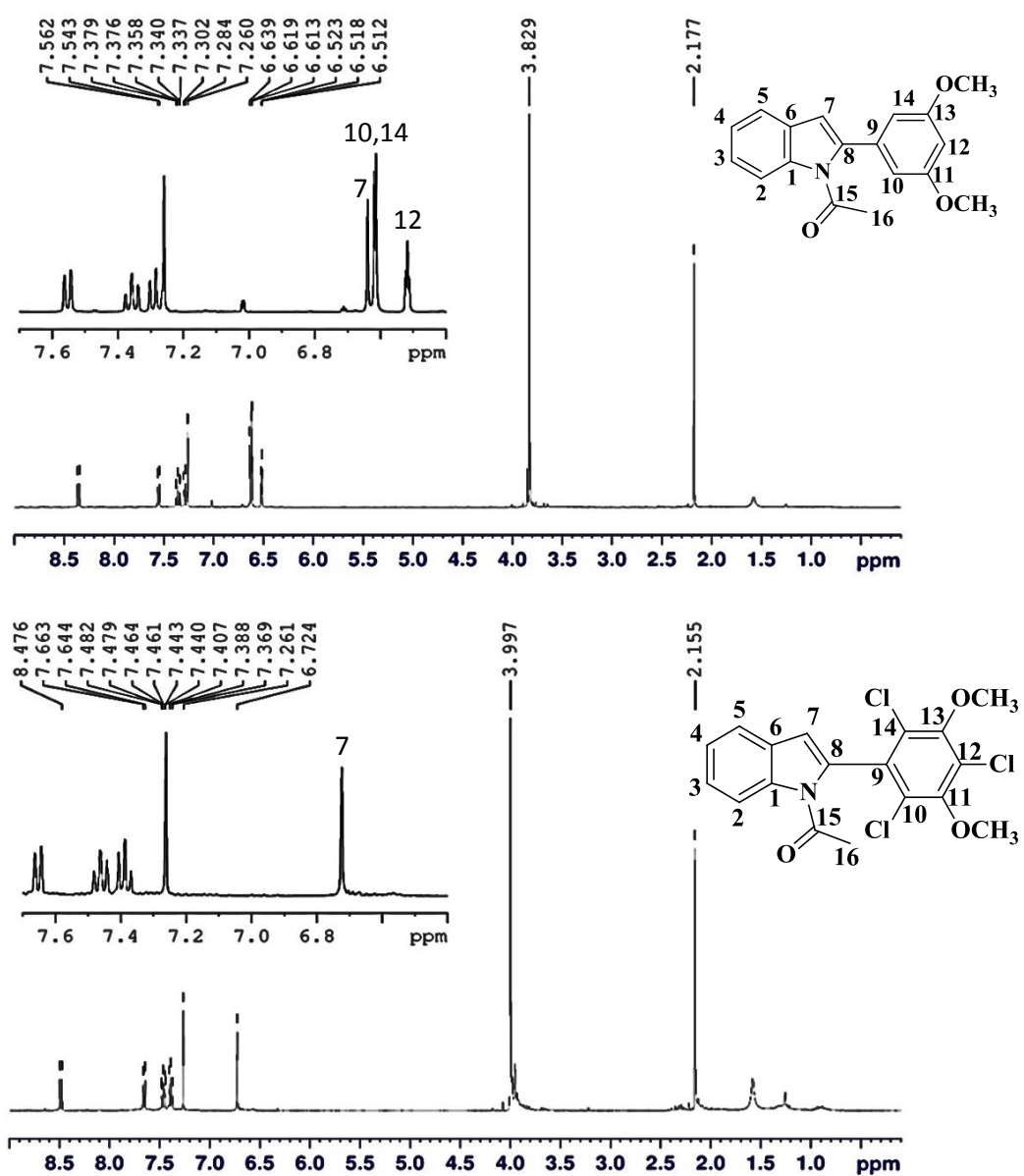


Figure 3.2: Comparison of ^1H NMR of indole 2.14 and 2.15

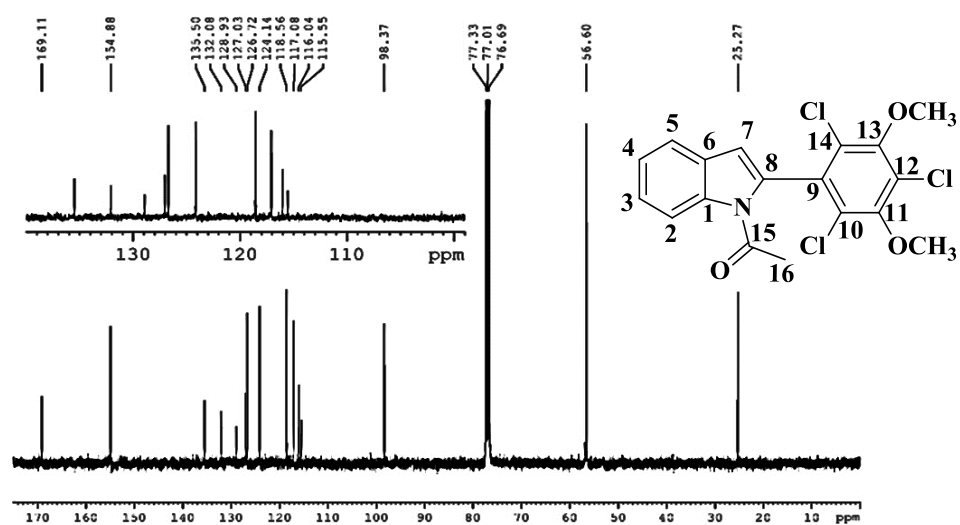
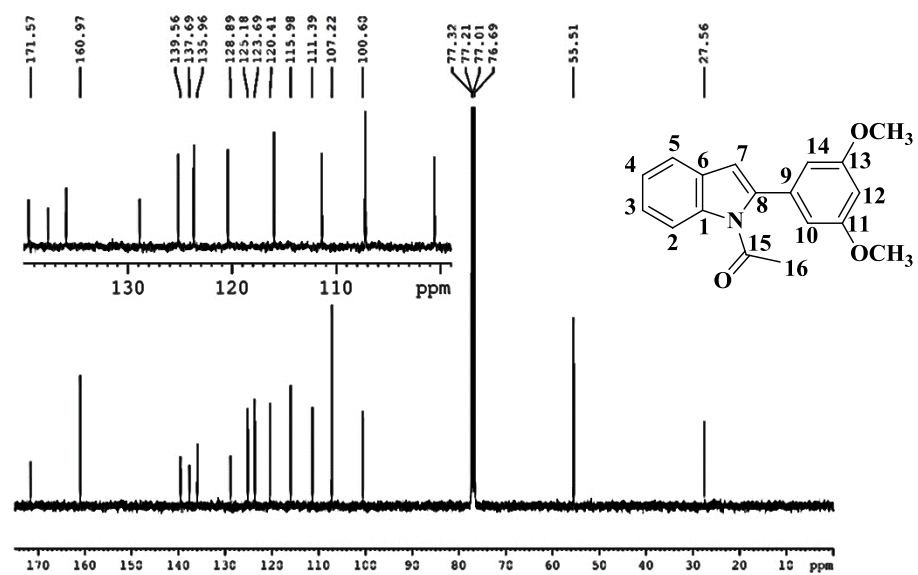
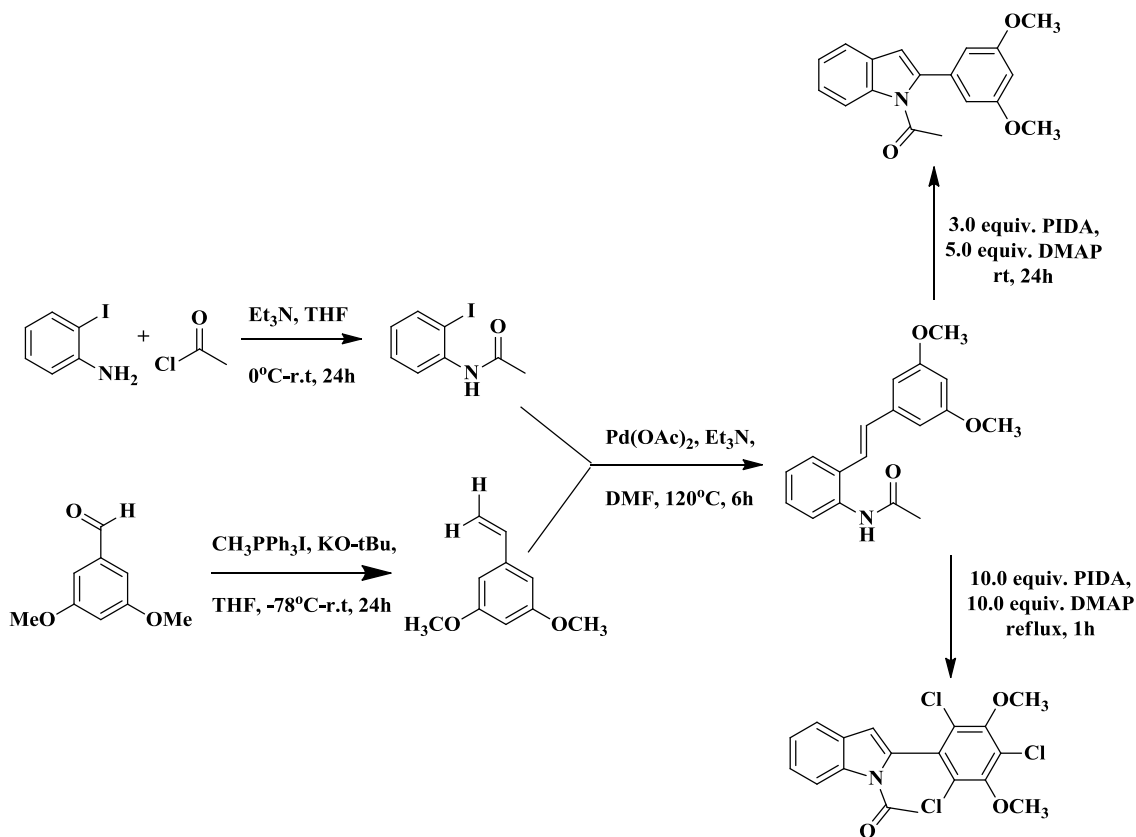


Figure 3.3: Comparison of ¹³C NMR of indole **2.14** and **2.15**

Chapter 4

4.0 Conclusion

Six *o*-amidostilbenes were prepared via an improved Heck coupling procedure (Scheme 3.3) with yields range from 59-68%. Four out of six stilbenes are structurally novel. The acetamidostilbene then was subjected to the PIDA oxidative cyclization to form the indole (**2.14**) with the presence of DMAP in DCM solvents. When the ratio of PIDA: DMAP: stilbene increase to 10:10:1, trichloro-indole **2.15** was obtained instead of indole **2.14**. Both **2.14** and **2.15**, novel indoles, were obtained in low yields (less than 10%). The oxidative cyclization is believed proceed via the formation of nitrenium ion as key intermediate.



Scheme 4.1: Conclusion for indole synthesis

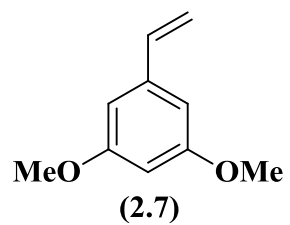
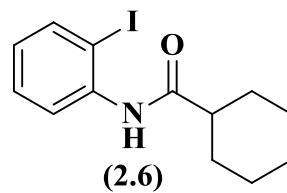
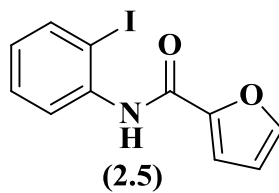
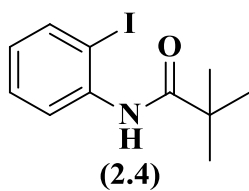
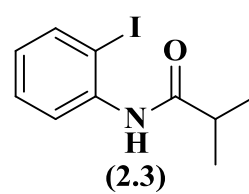
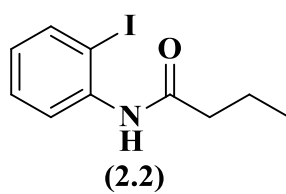
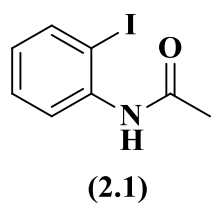


Figure 4.1: List of starting materials

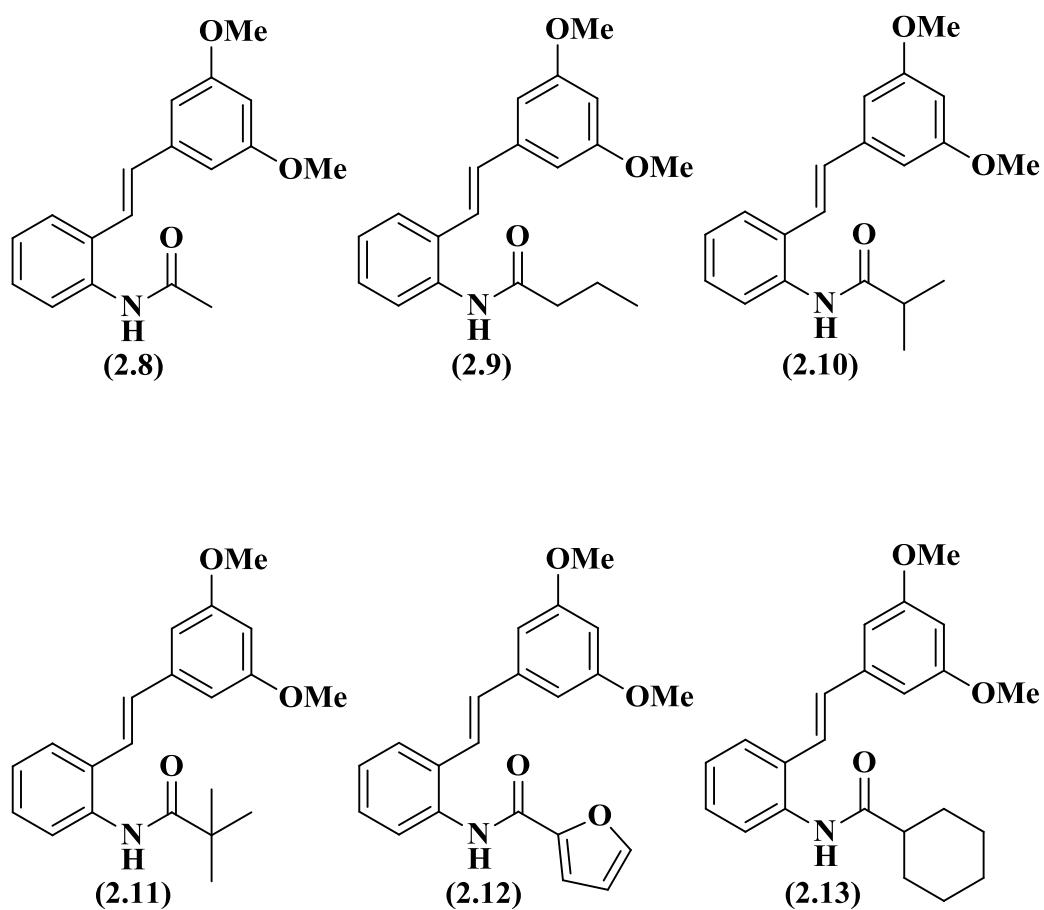


Figure 4.2: List of stilbenes

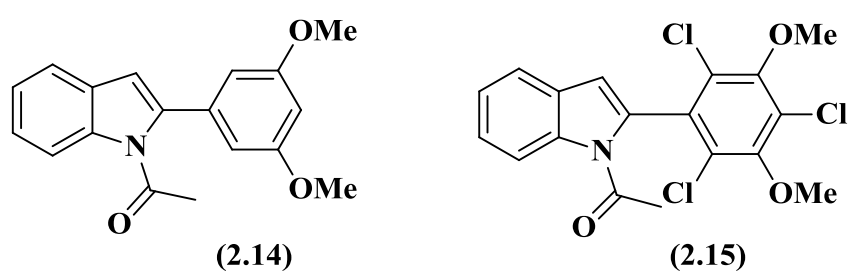


Figure 4.3: List of indoles synthesized

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Appendices

NMR Spectra of the Synthesized Compounds

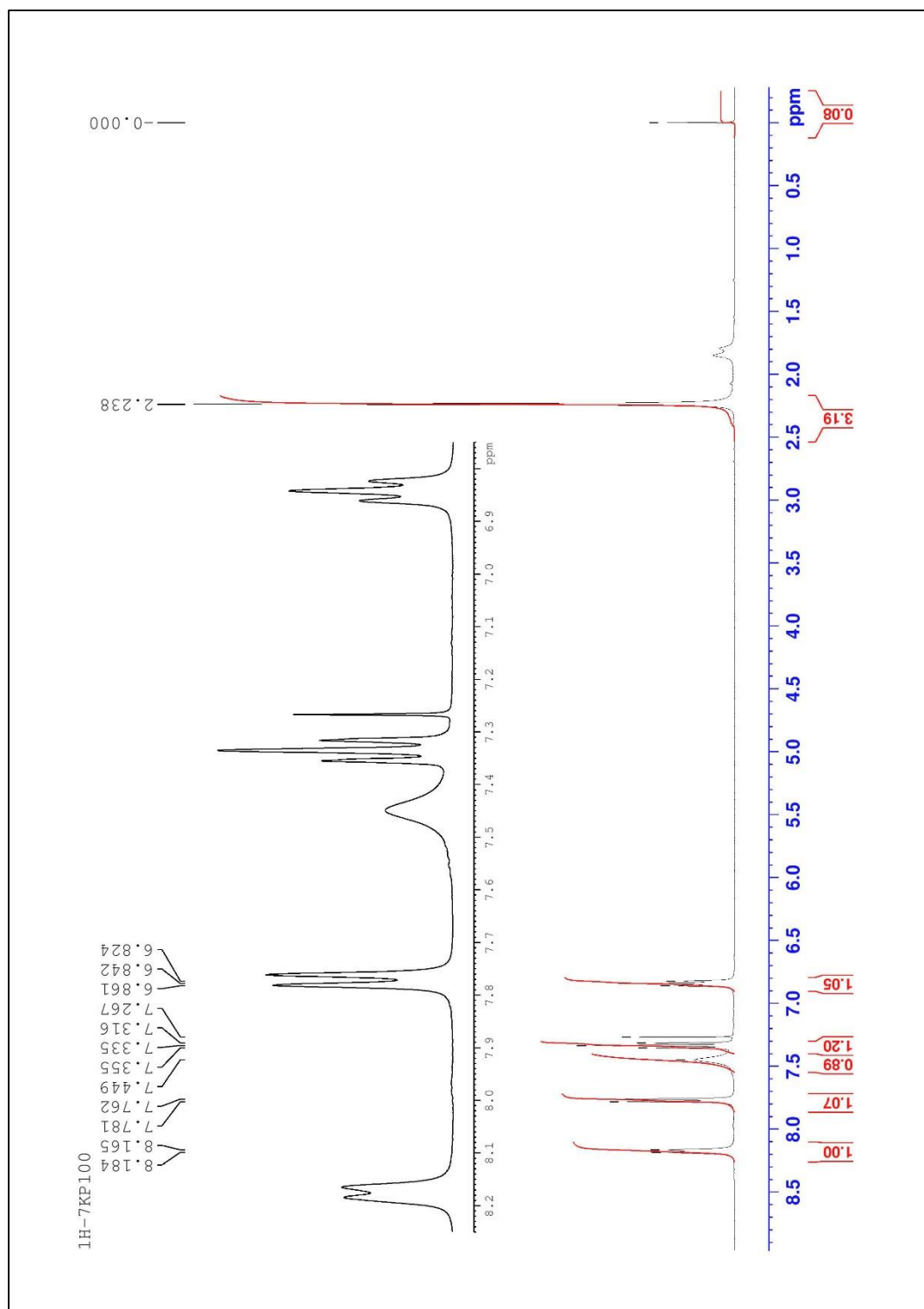


Figure A.1: ^1H spectrum (CDCl_3 , 400 MHz) of **2.1**

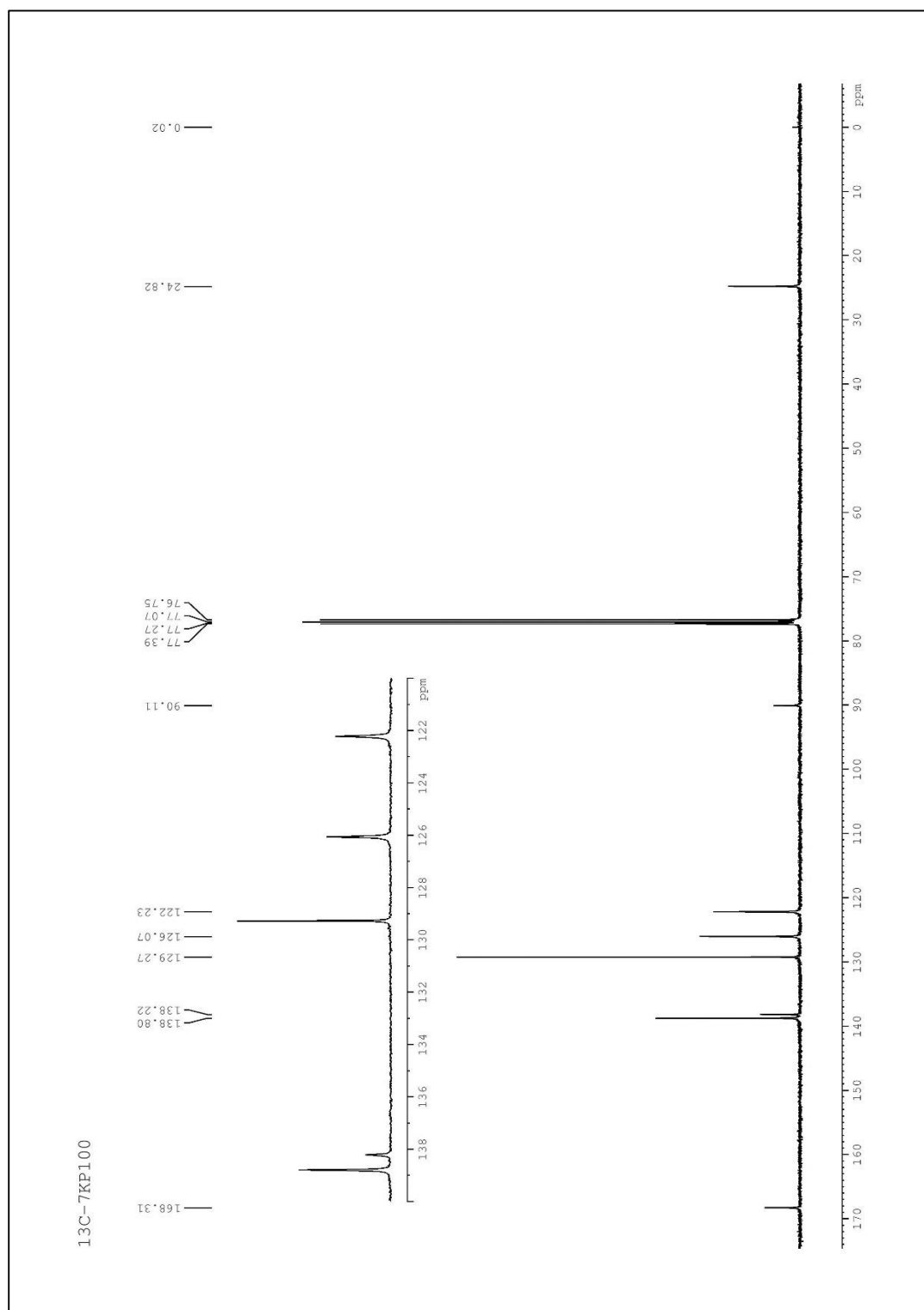


Figure A.2: ¹³C spectrum (CDCl₃, 100 MHz) of **2.1**

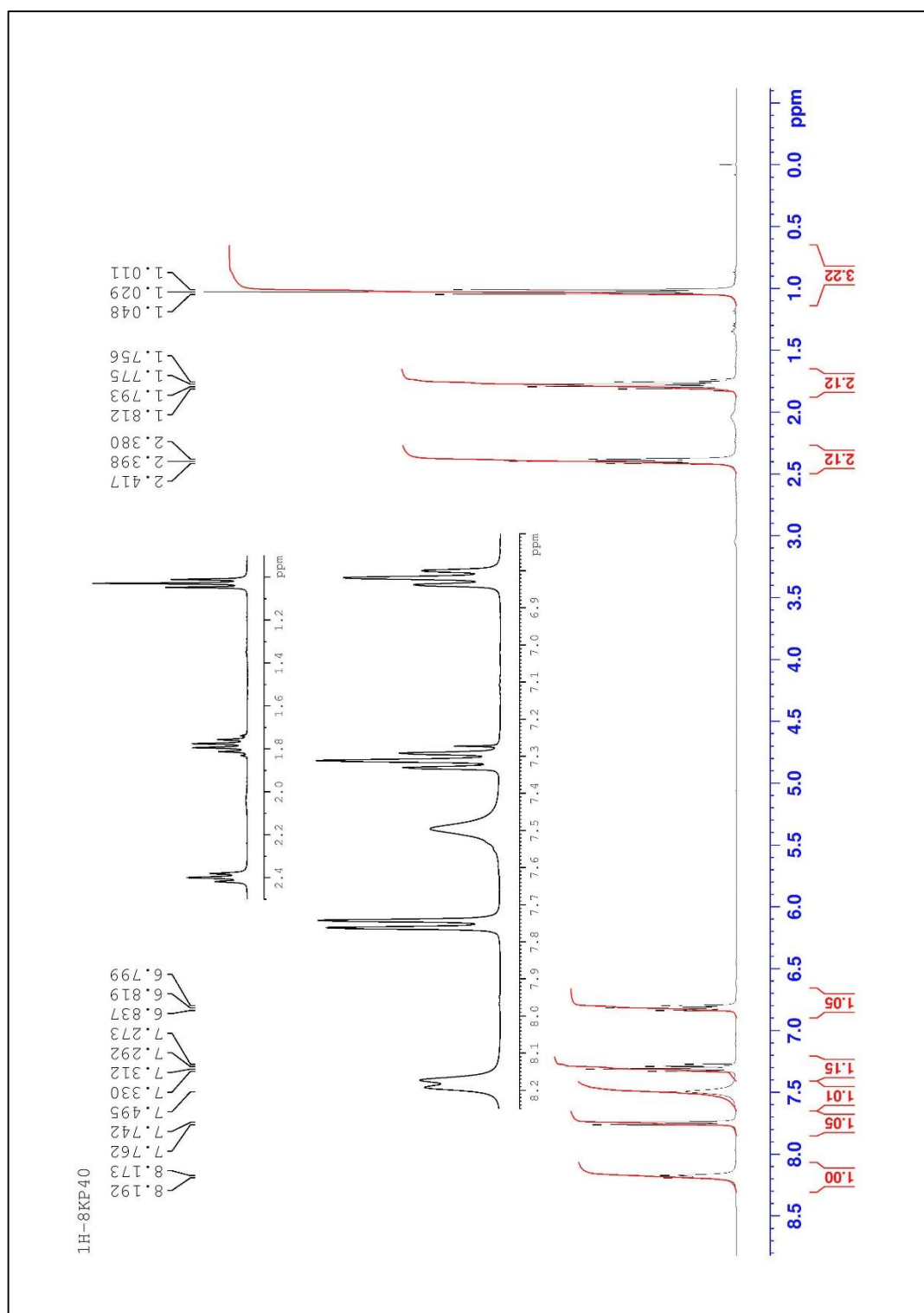


Figure A.3: ^1H spectrum (CDCl_3 , 400 MHz) of **2.2**

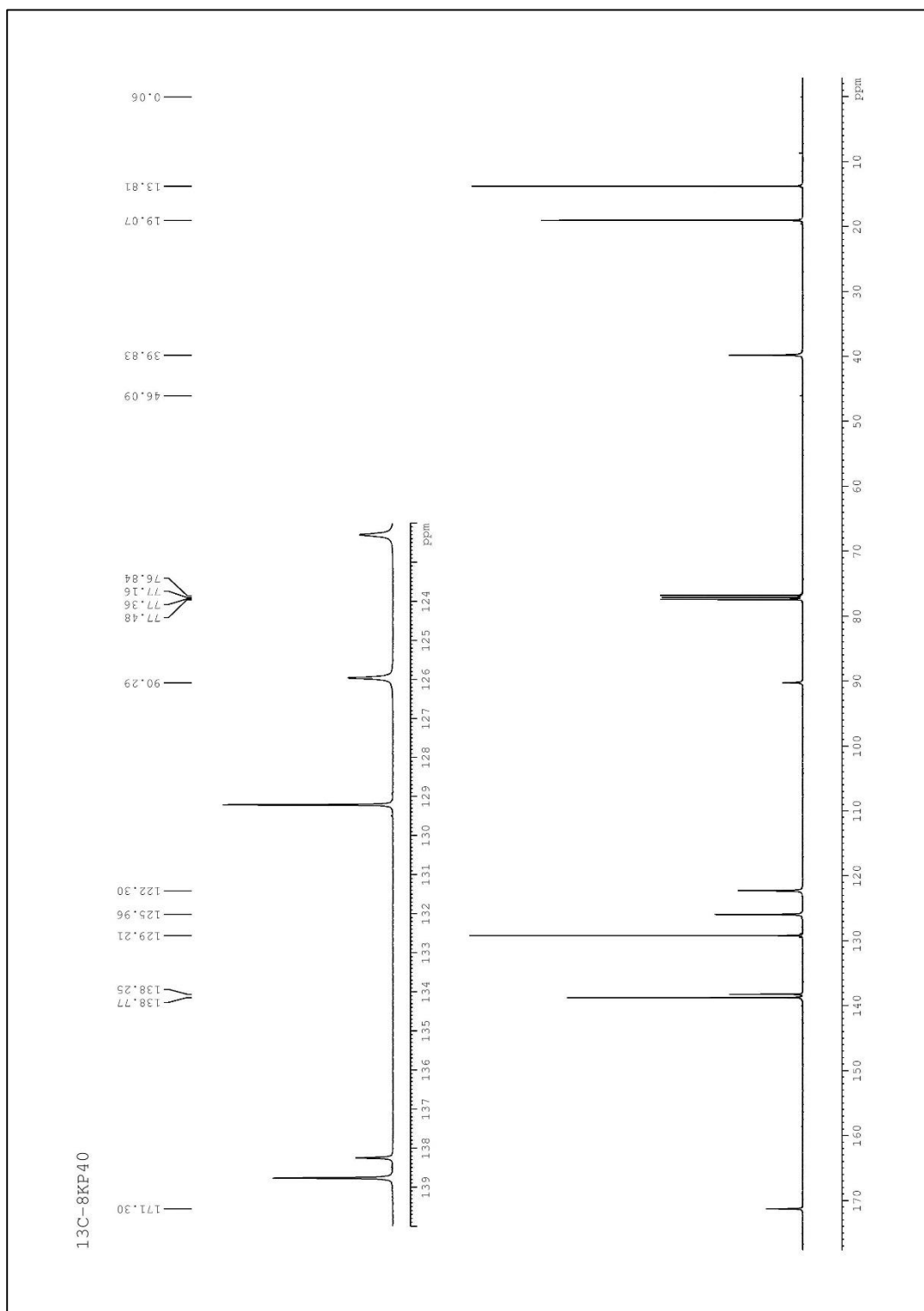


Figure A.4: ¹³C spectrum (CDCl₃, 100 MHz) of **2.2**

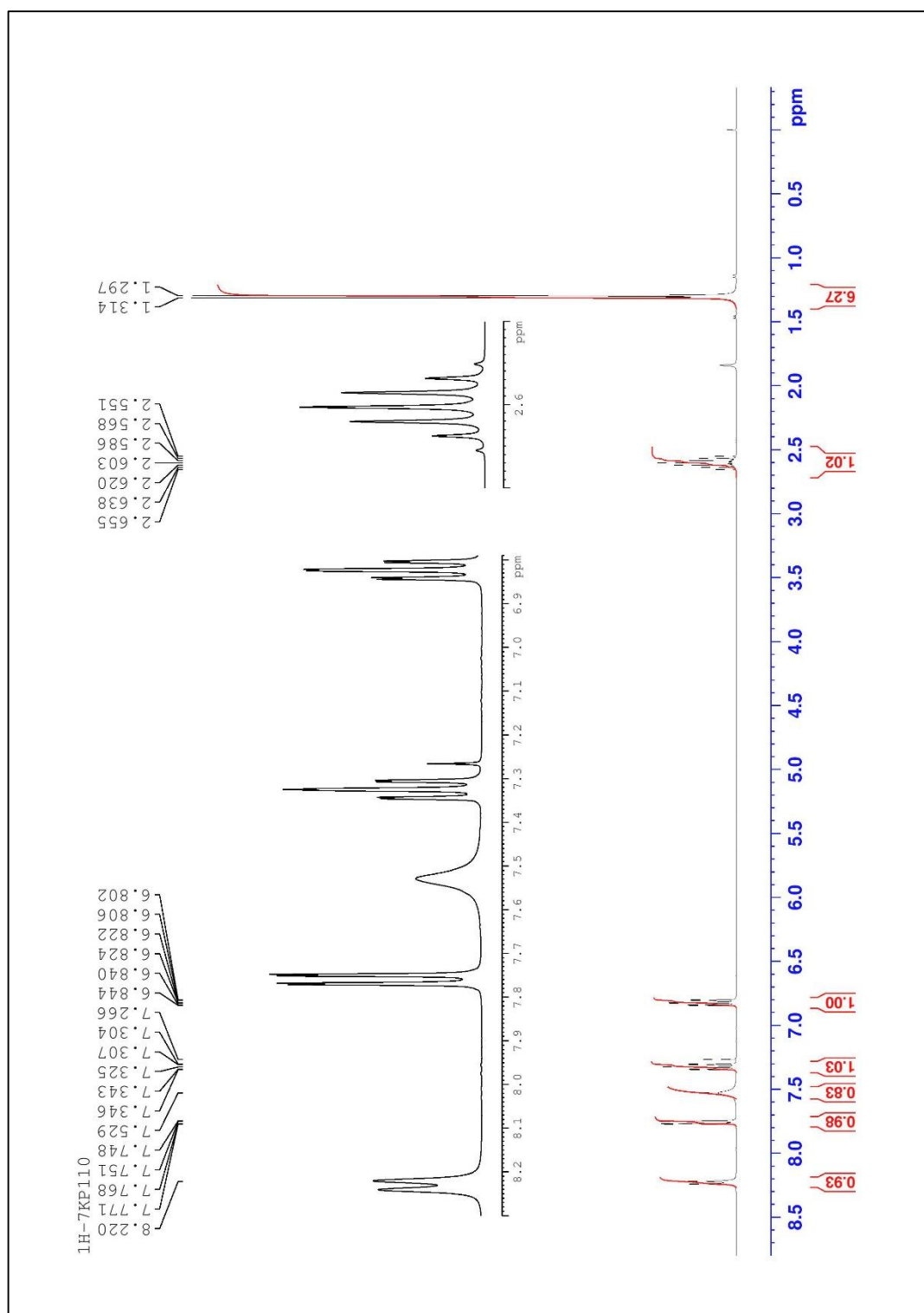


Figure A.5: ¹H spectrum (CDCl₃, 400 MHz) of **2.3**

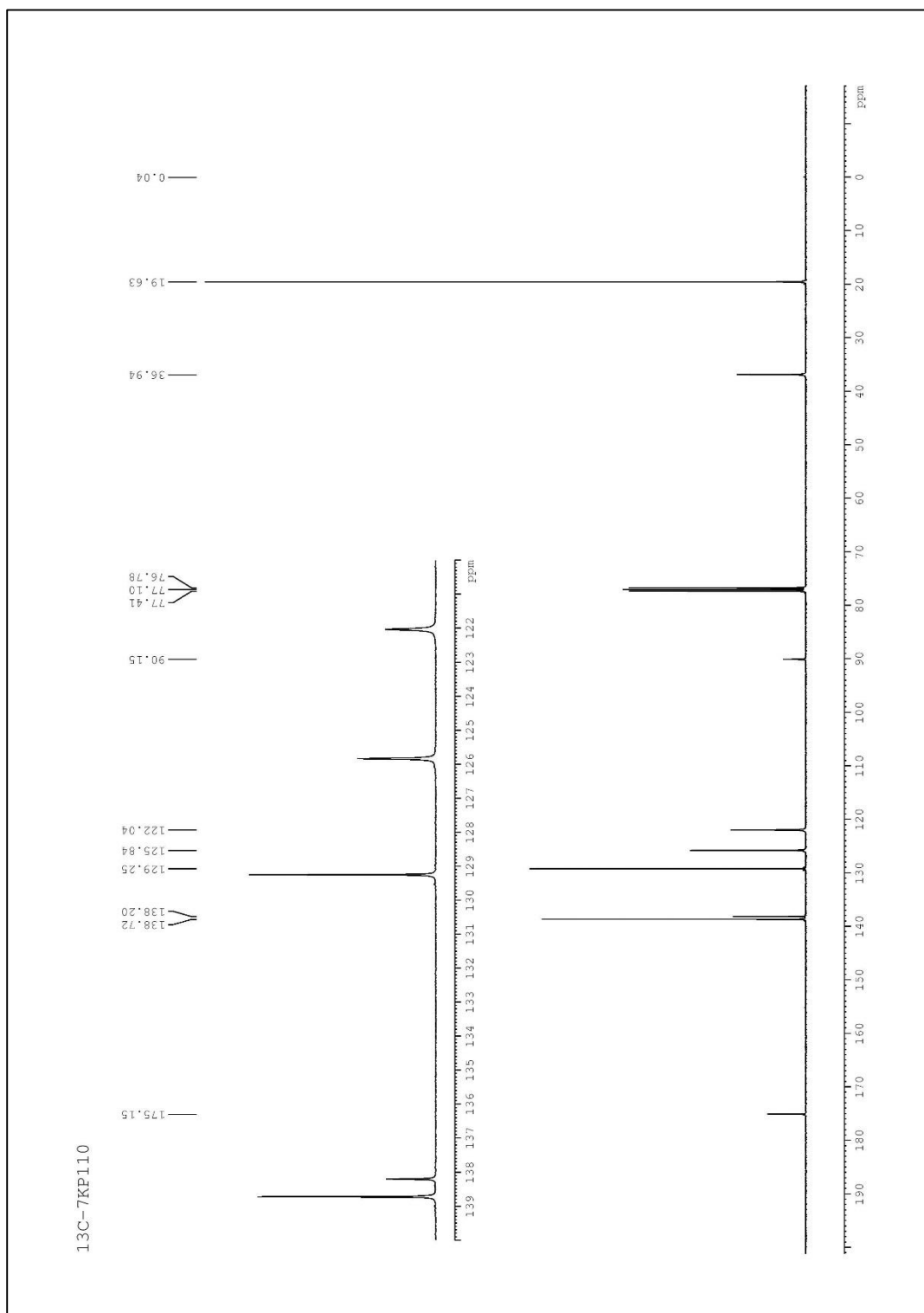


Figure A.6: ¹³C spectrum (CDCl₃, 100 MHz) of **2.3**

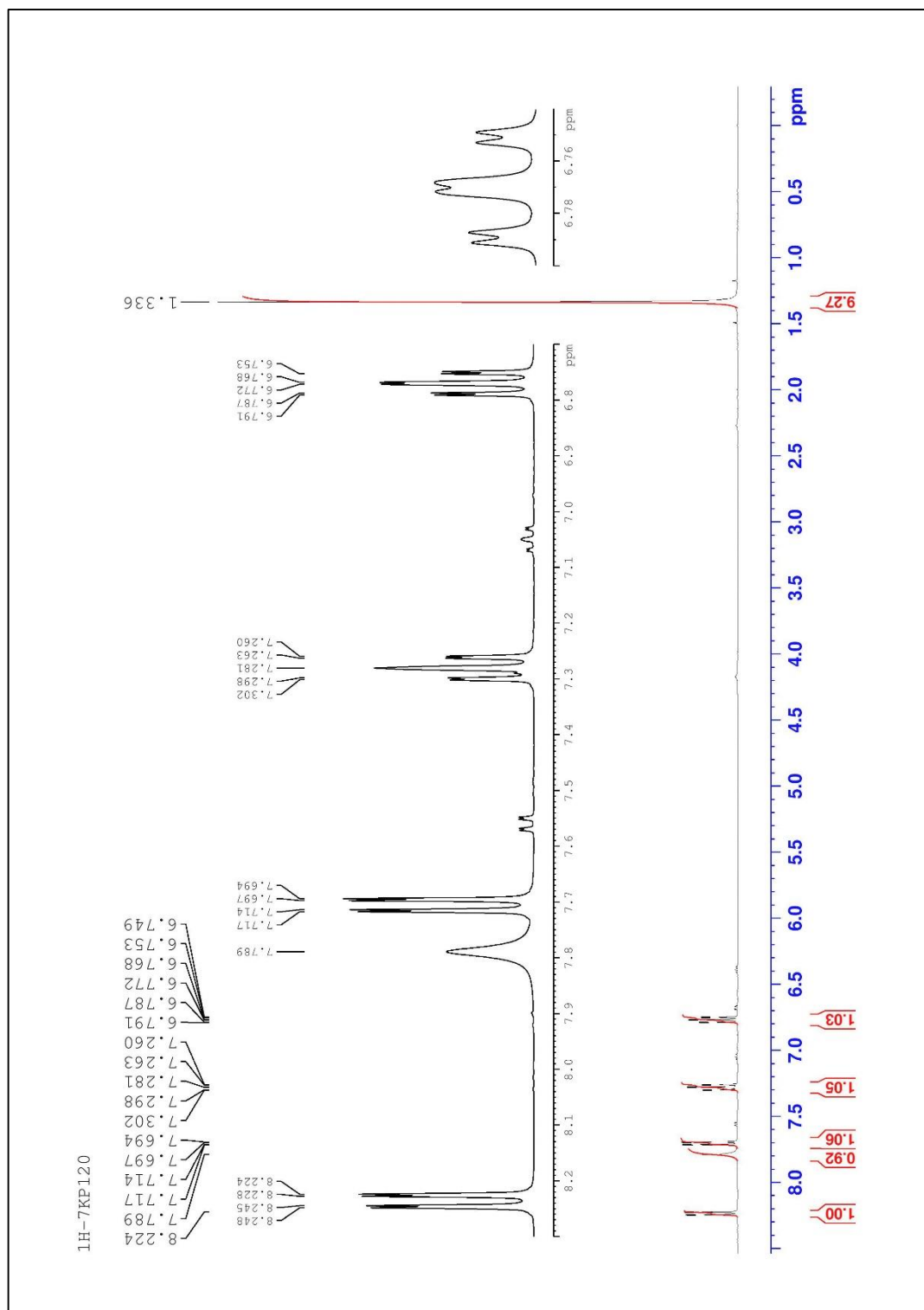


Figure A.7: ¹H spectrum (CDCl₃, 400 MHz) of **2.4**

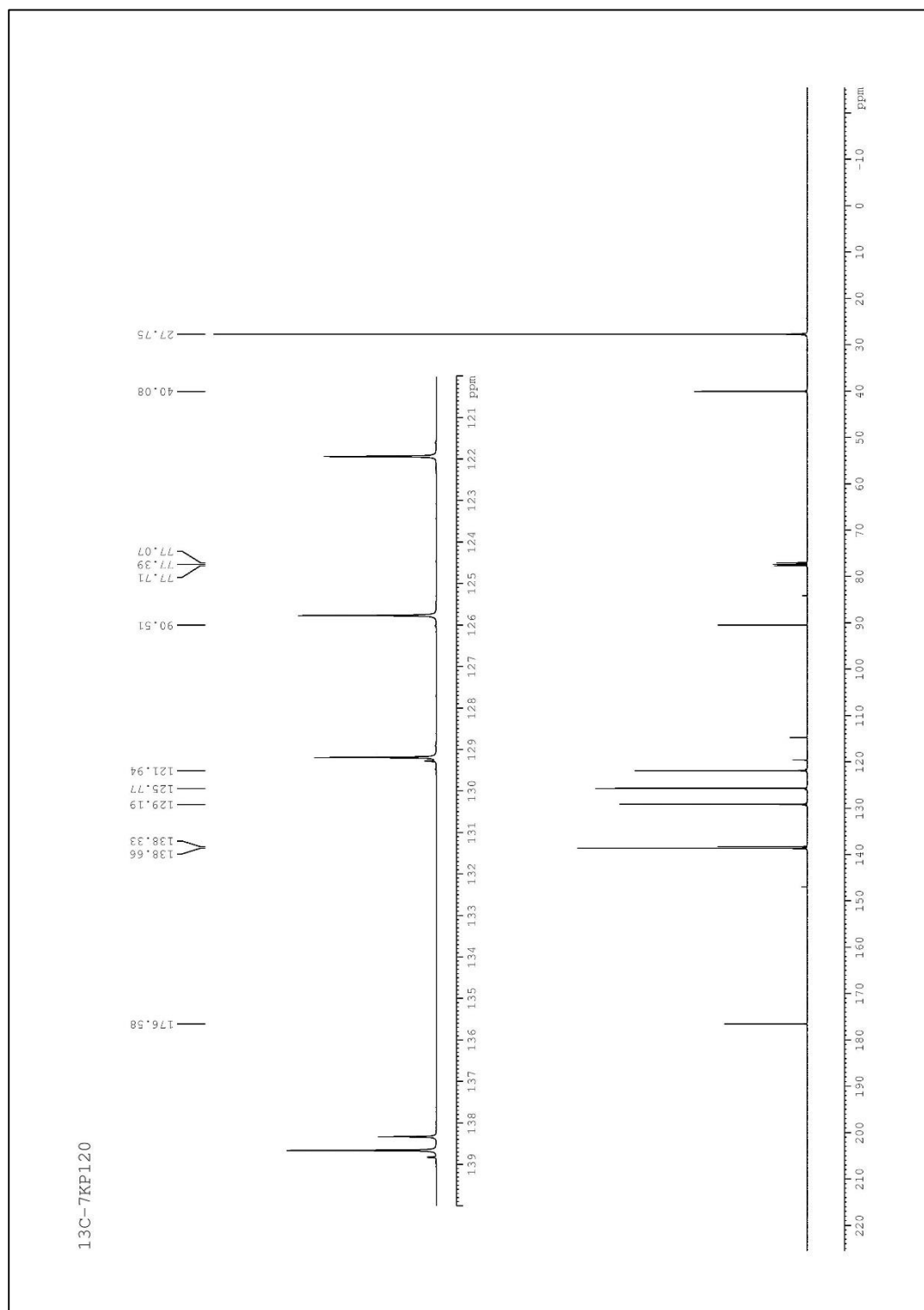


Figure A.8: ¹³C spectrum (CDCl₃, 100 MHz) of **2.4**

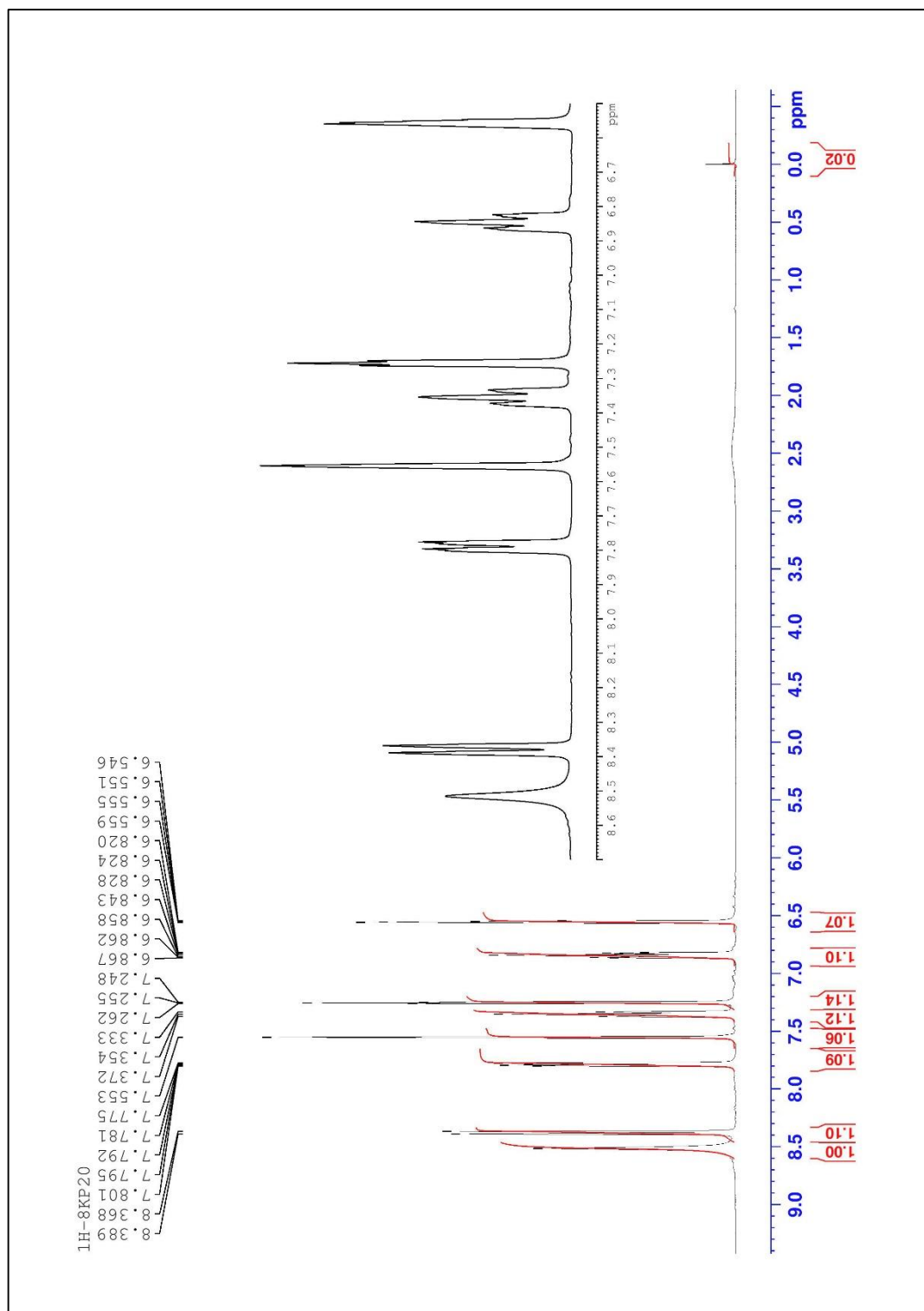


Figure A.9: ¹H spectrum (CDCl₃, 400 MHz) of **2.5**

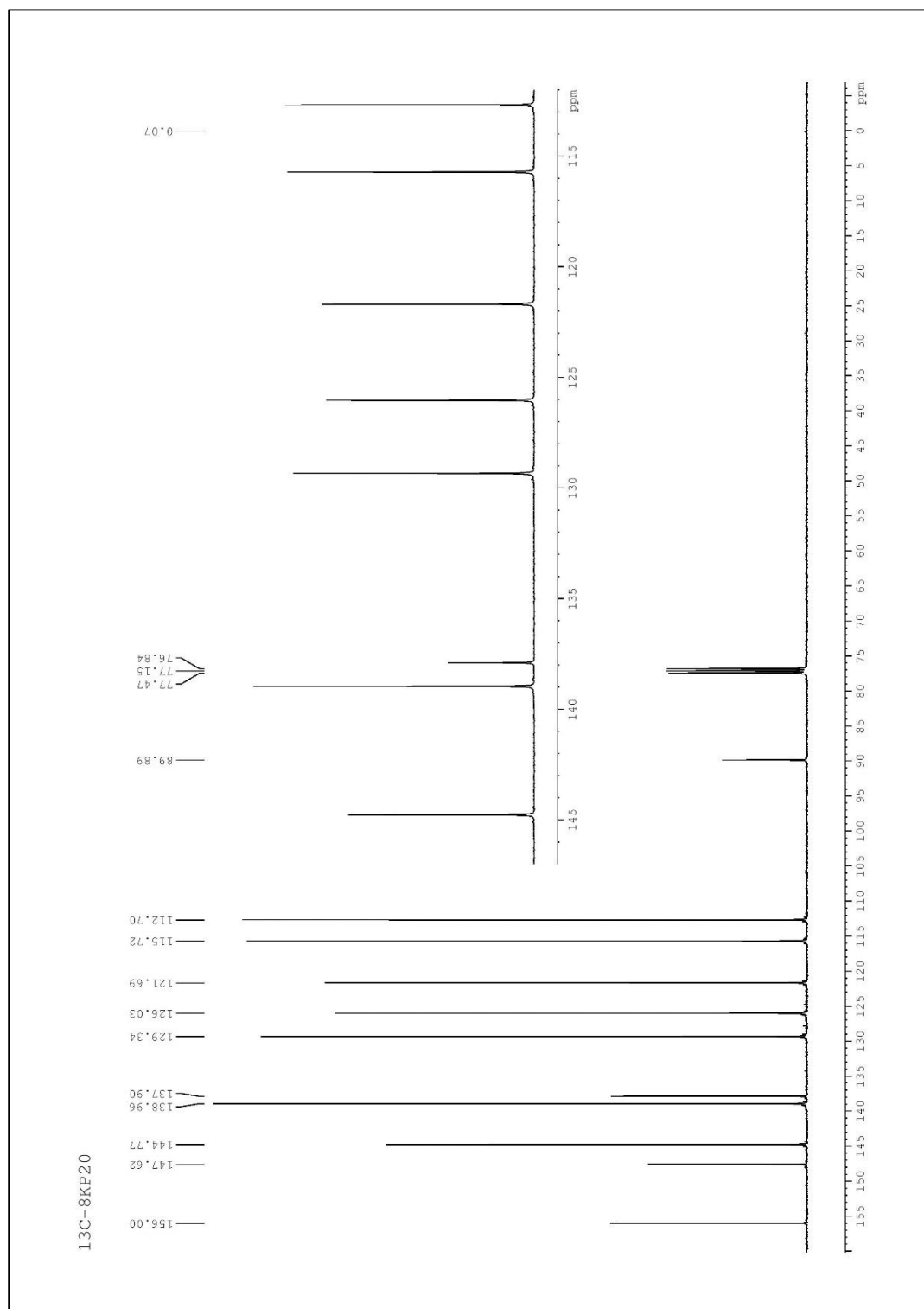


Figure A.10: ^{13}C spectrum (CDCl_3 , 100 MHz) of **2.5**

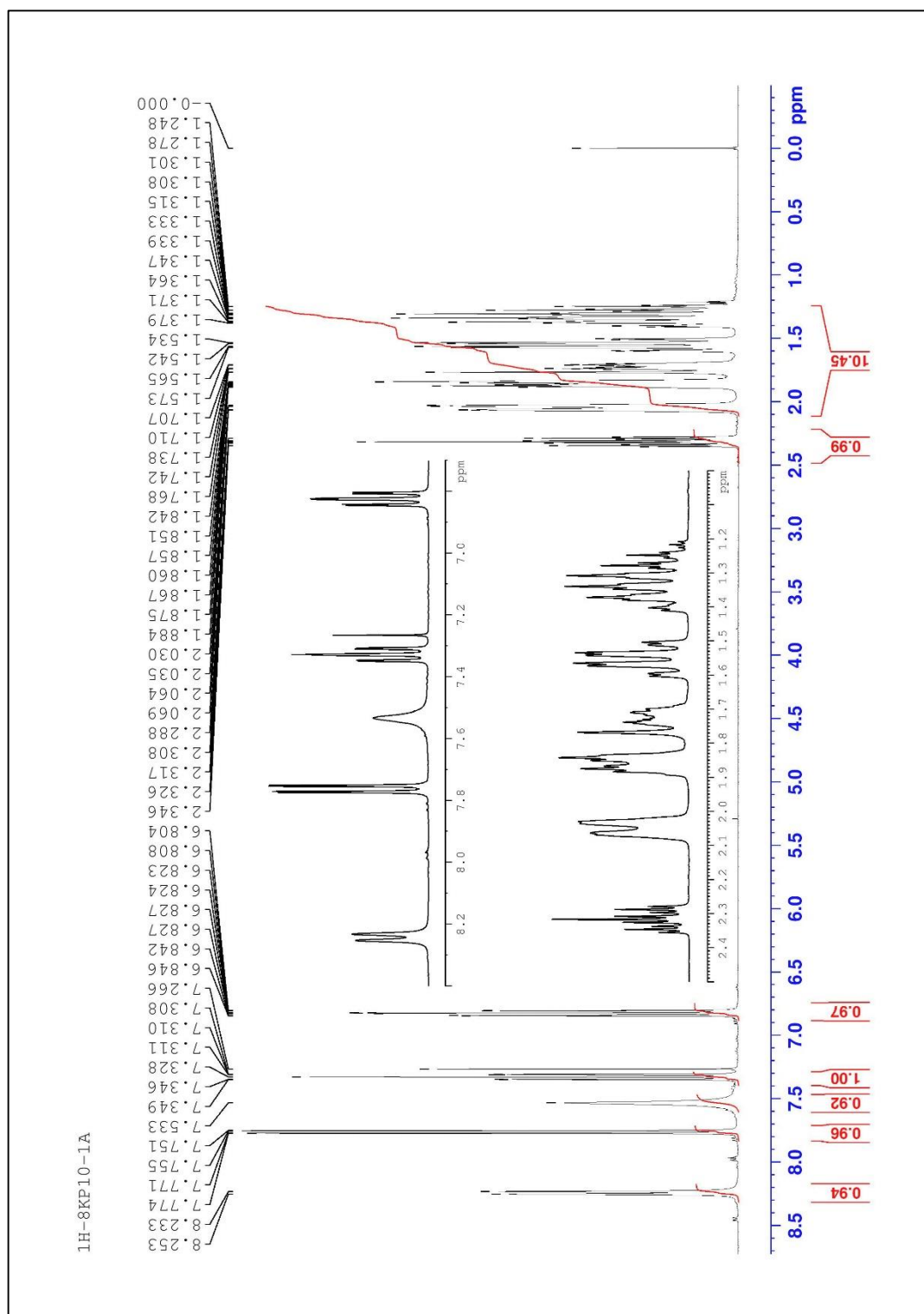


Figure A.11: ^1H spectrum (CDCl_3 , 400 MHz) of **2.6**

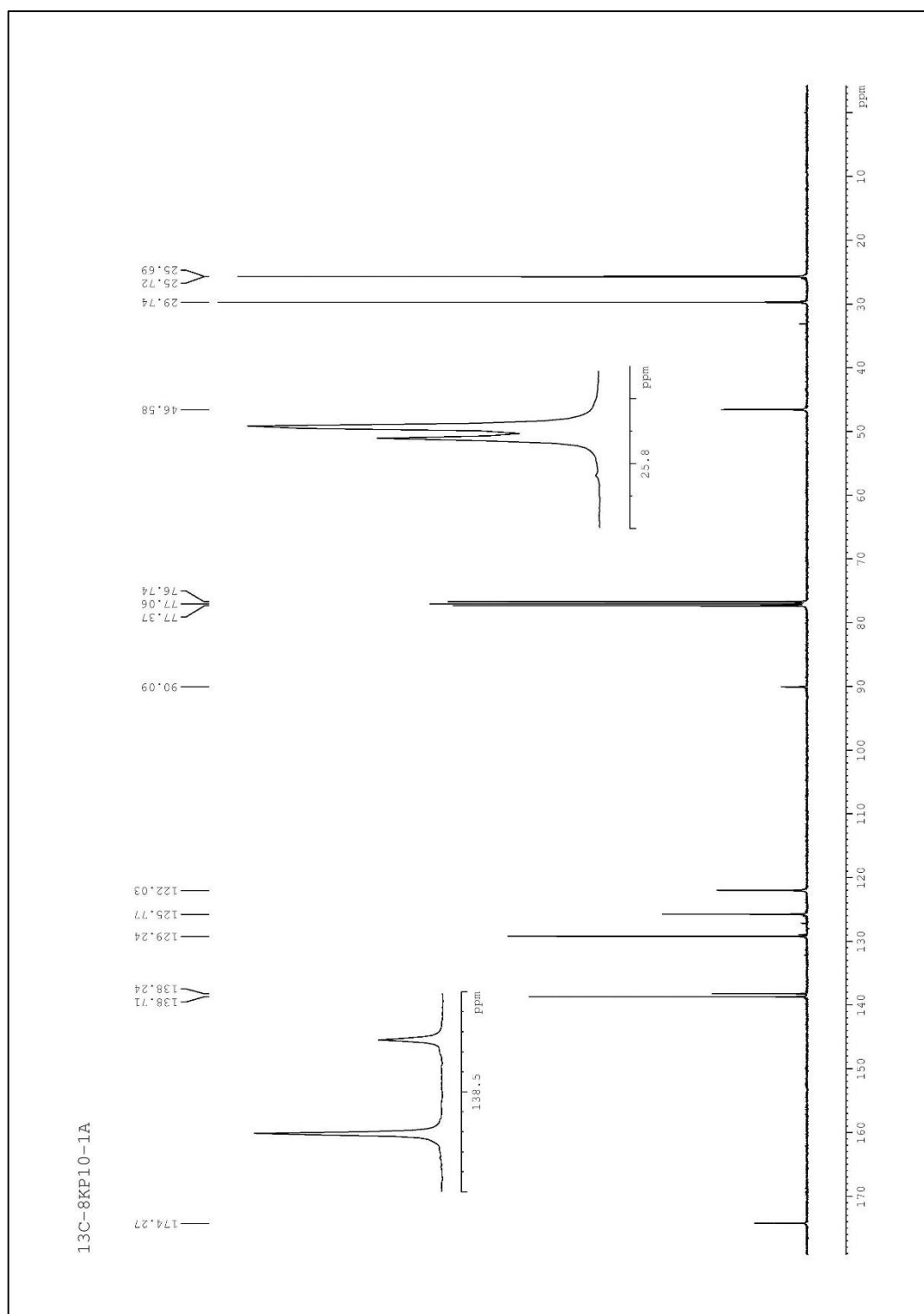


Figure A.12: ^{13}C spectrum (CDCl_3 , 100 MHz) of **2.6**

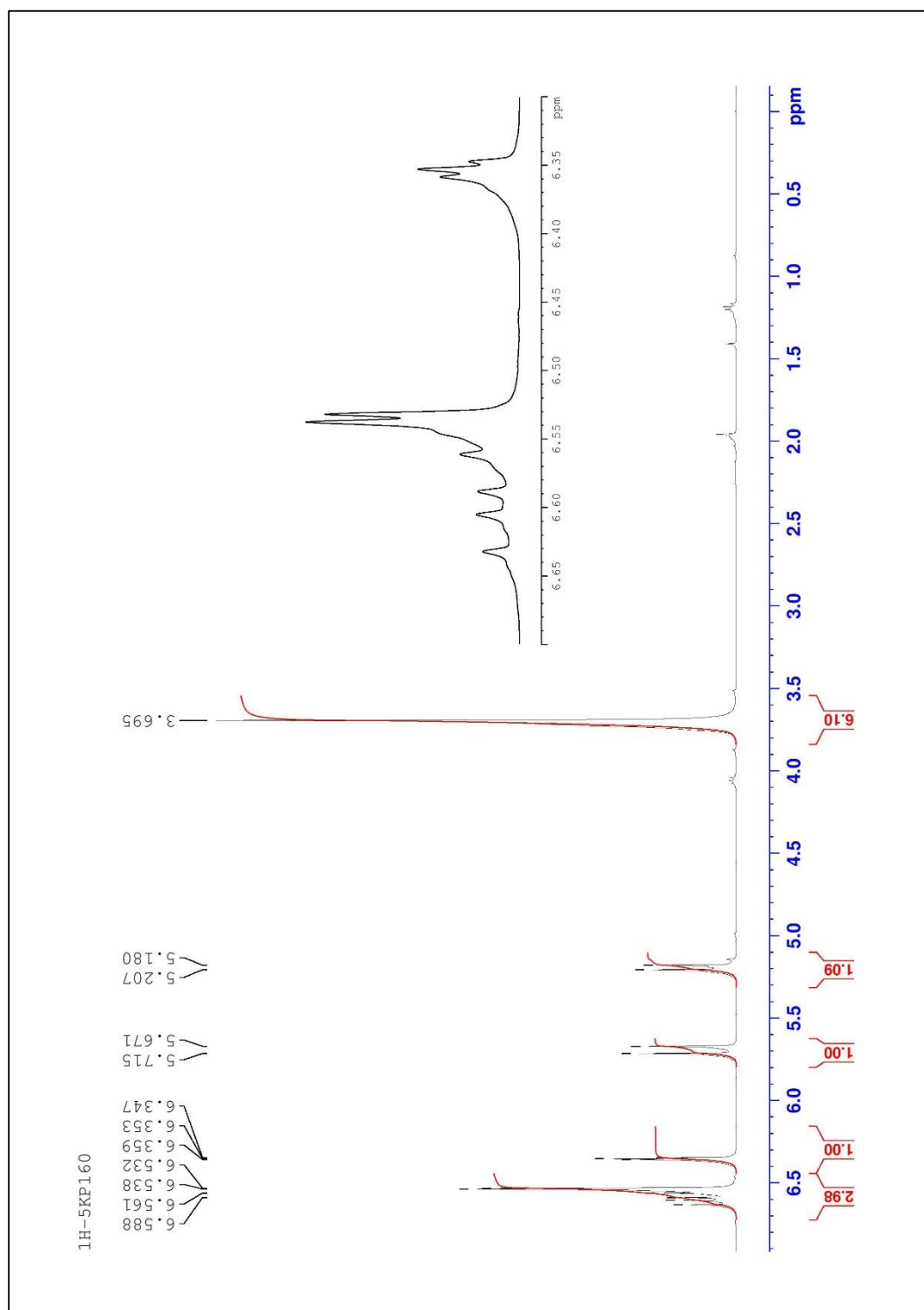


Figure A.13: ¹H spectrum (CDCl₃, 400 MHz) of **2.7**

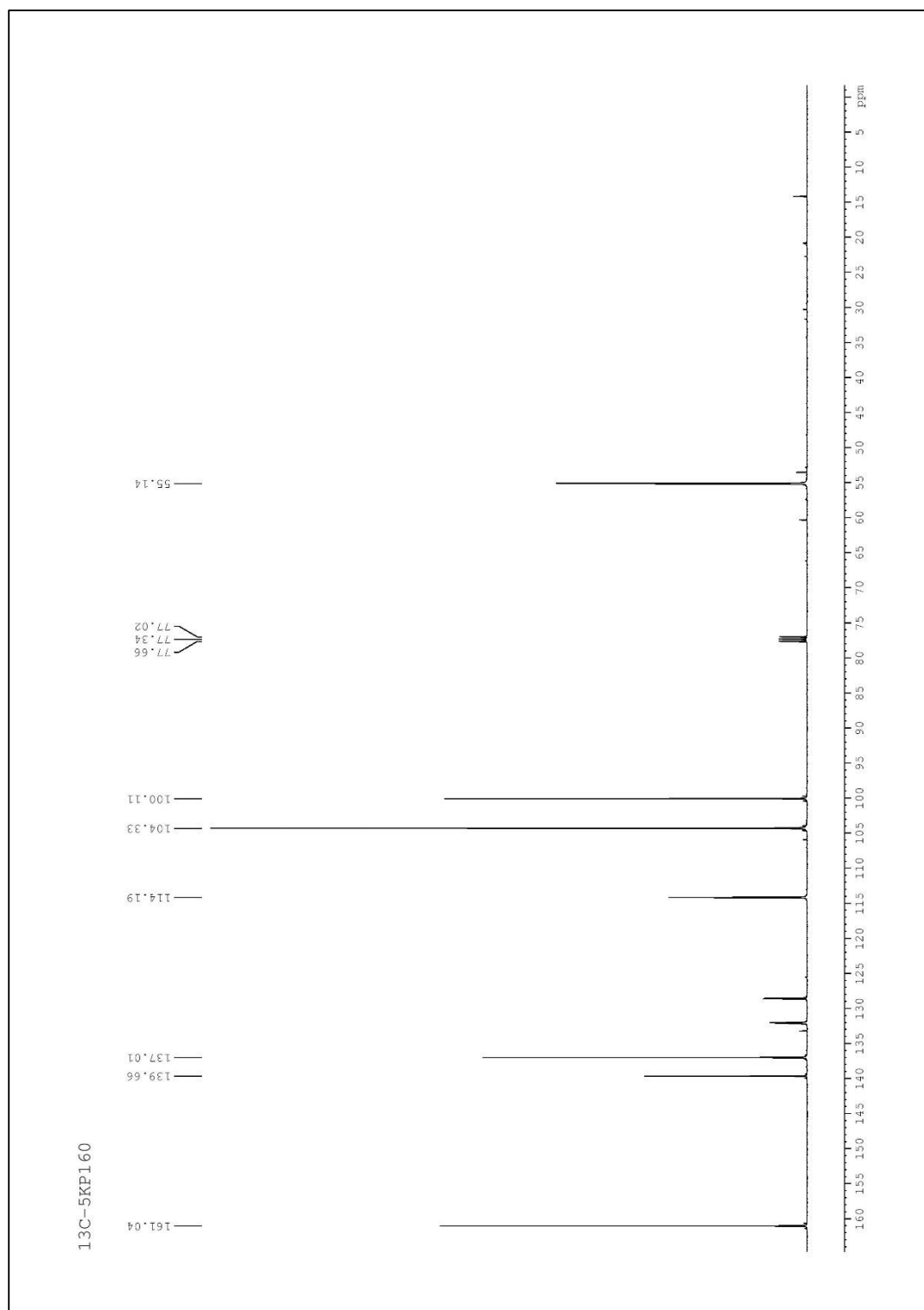


Figure A.14: ^{13}C spectrum (CDCl_3 , 100 MHz) of **2.6**

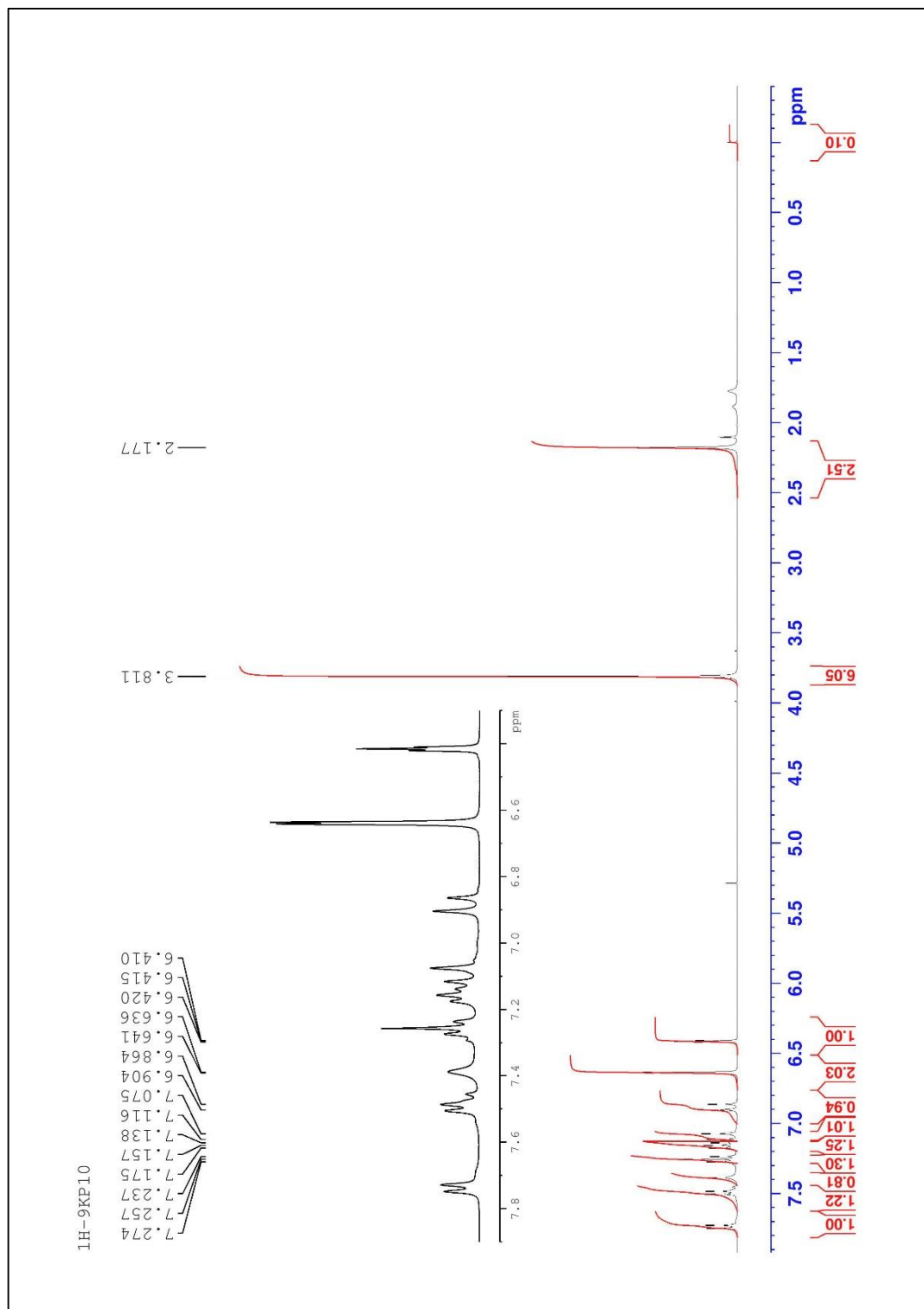


Figure A.15: ¹H spectrum (CDCl₃, 400 MHz) of **2.8**

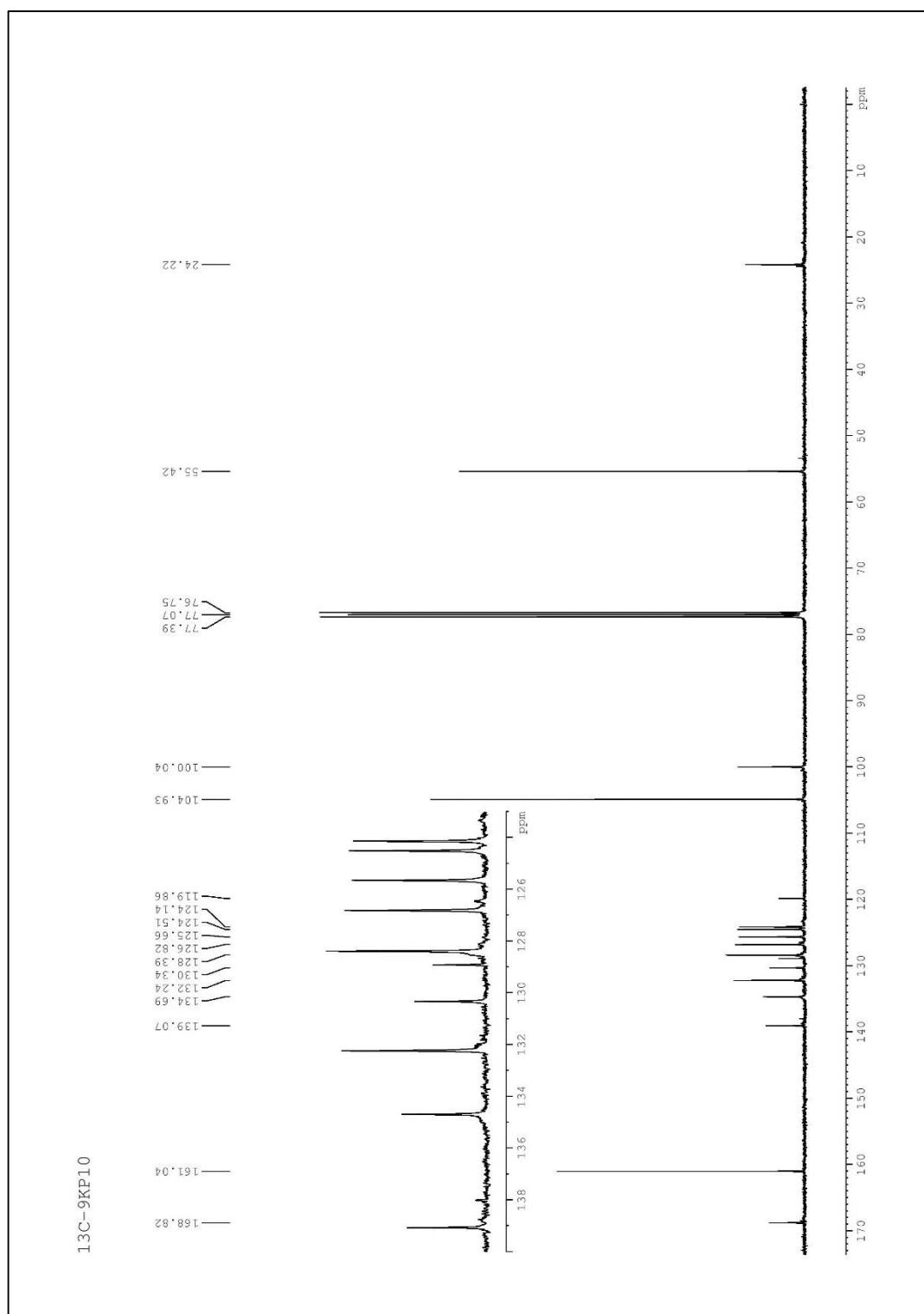


Figure A.16: ¹³C spectrum (CDCl₃, 100 MHz) of **2.8**

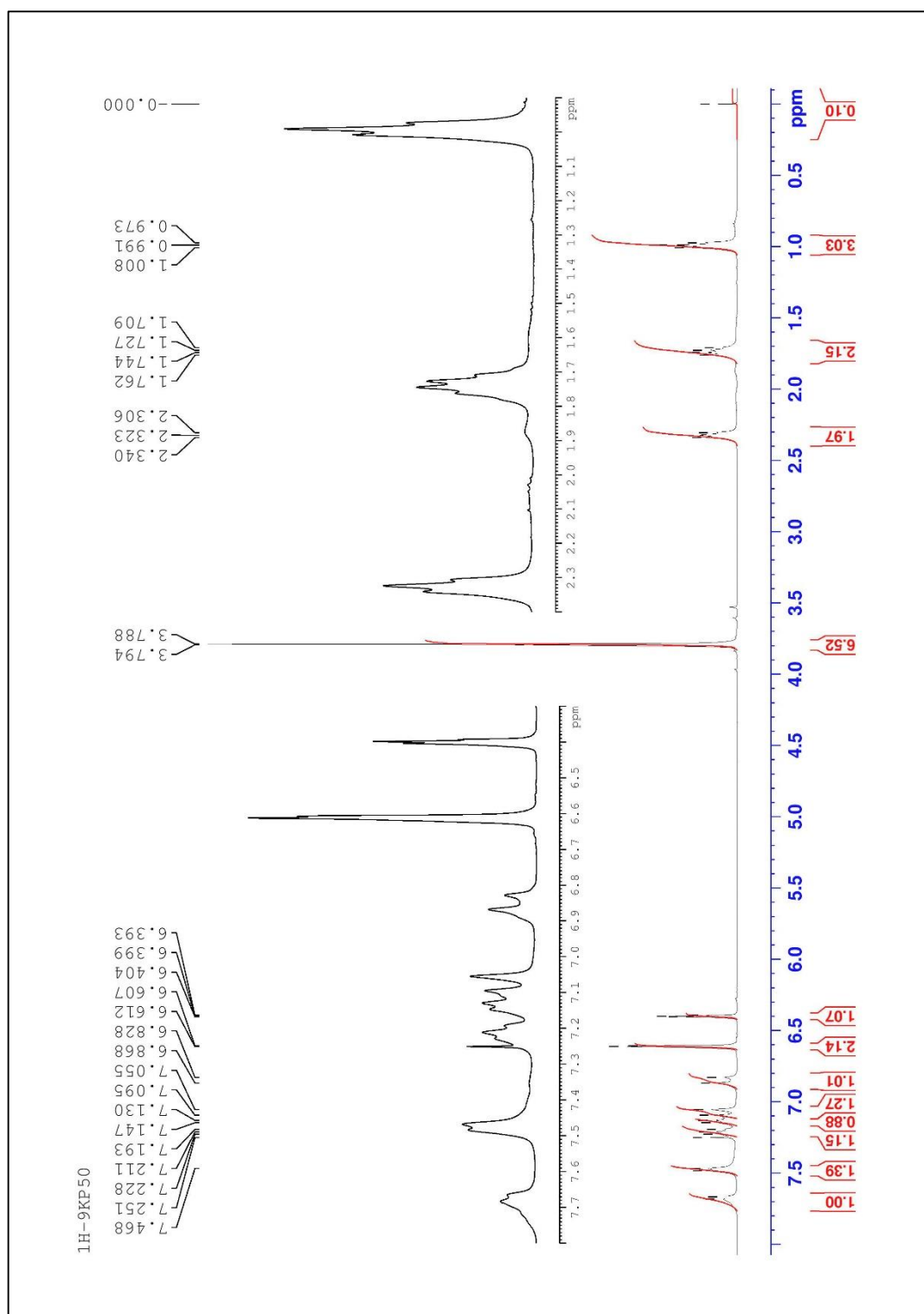


Figure A.17: ¹H spectrum (CDCl₃, 400 MHz) of **2.9**

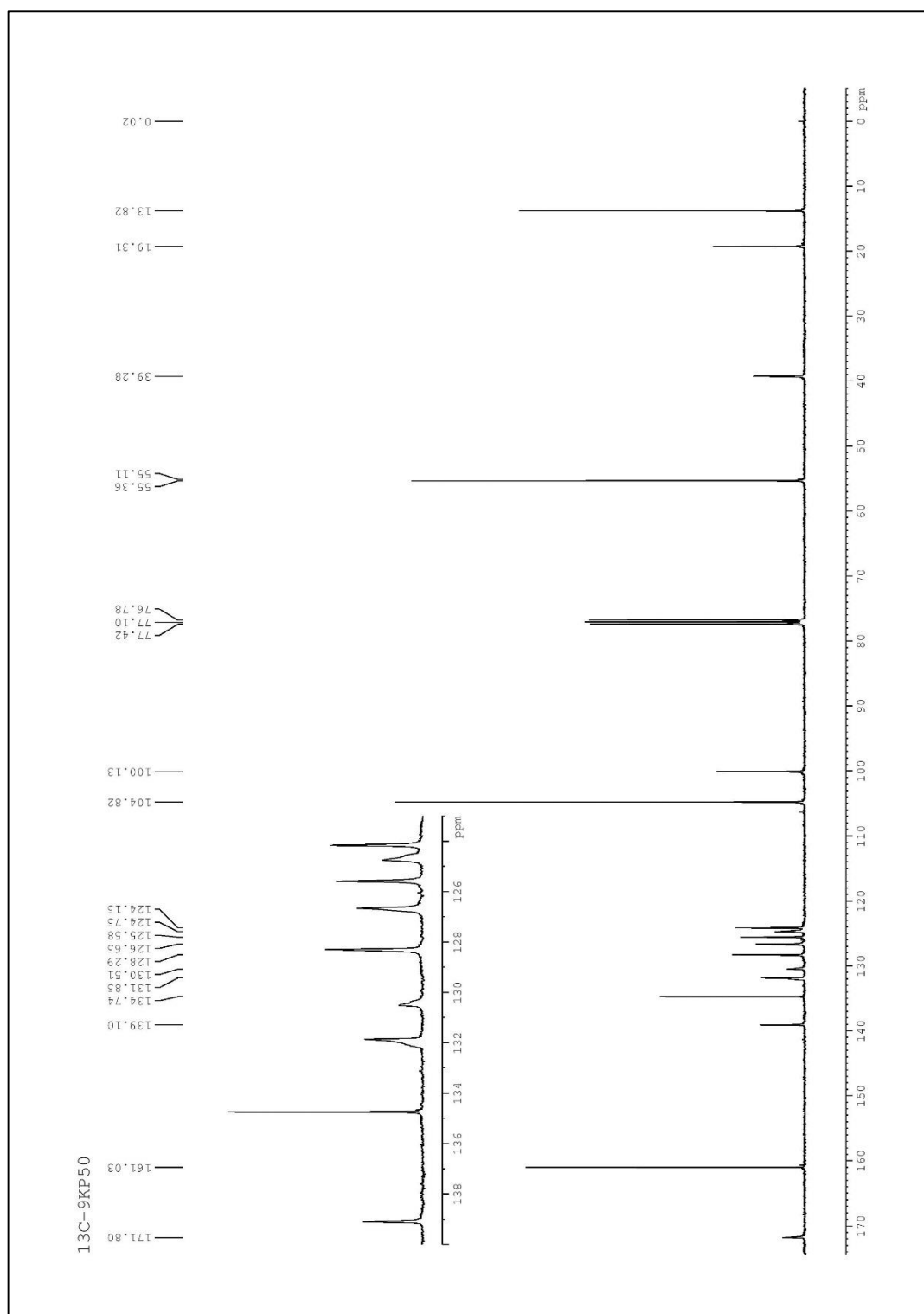


Figure A.18: ^{13}C spectrum (CDCl_3 , 100 MHz) of **2.9**

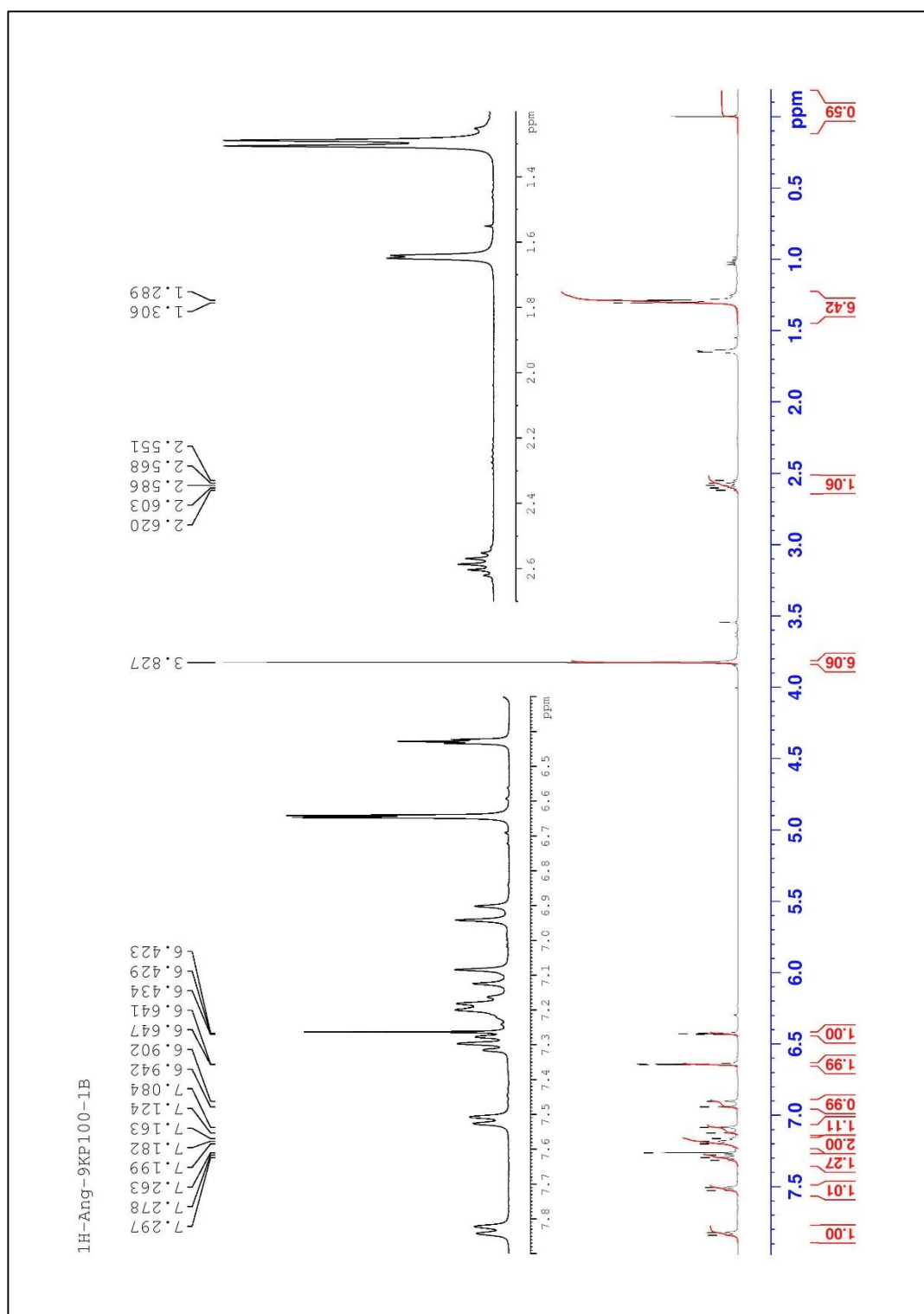


Figure A.19: ¹H spectrum (CDCl₃, 400 MHz) of **2.10**

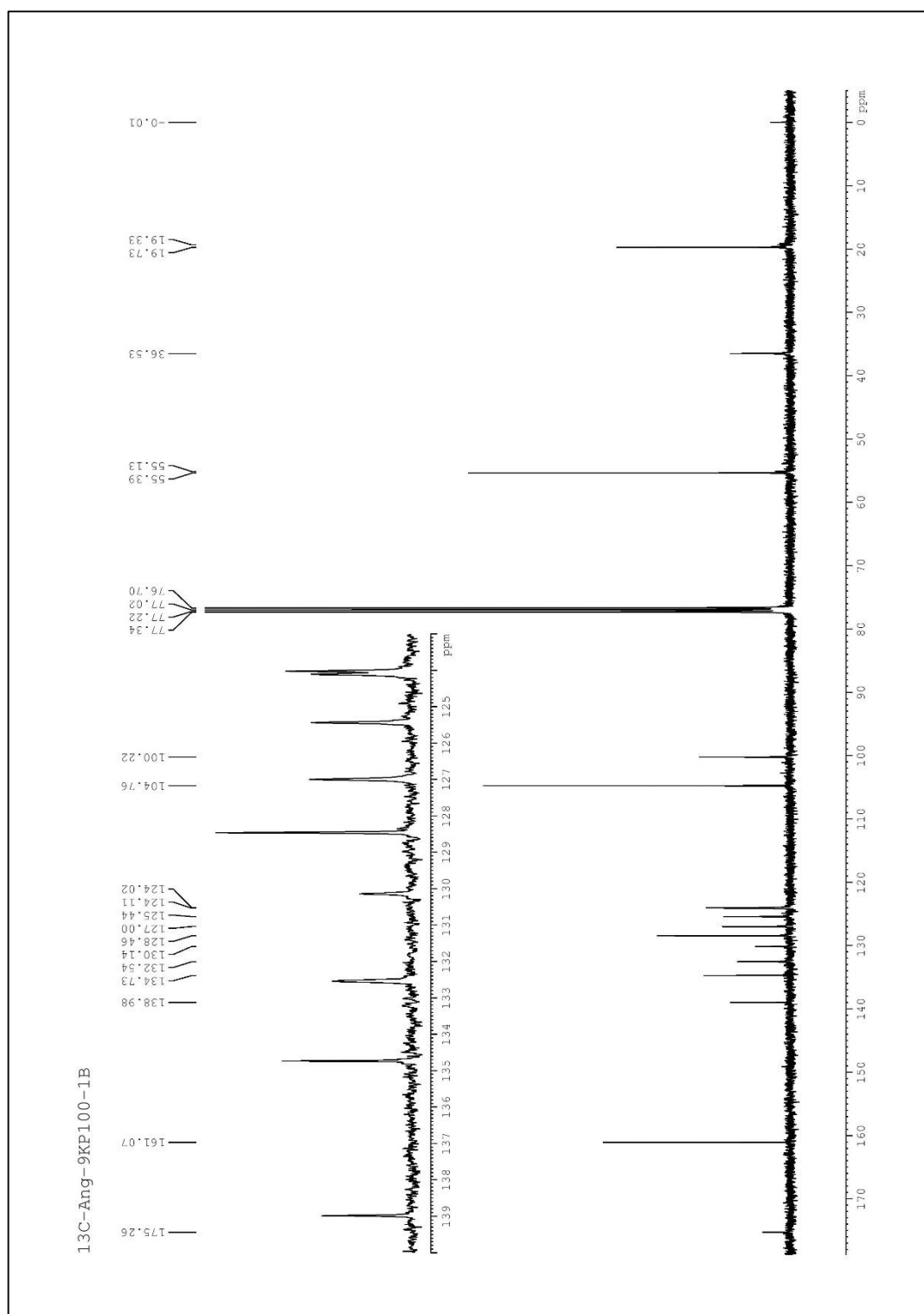


Figure A.20: ¹³C spectrum (CDCl₃, 100 MHz) of **2.10**

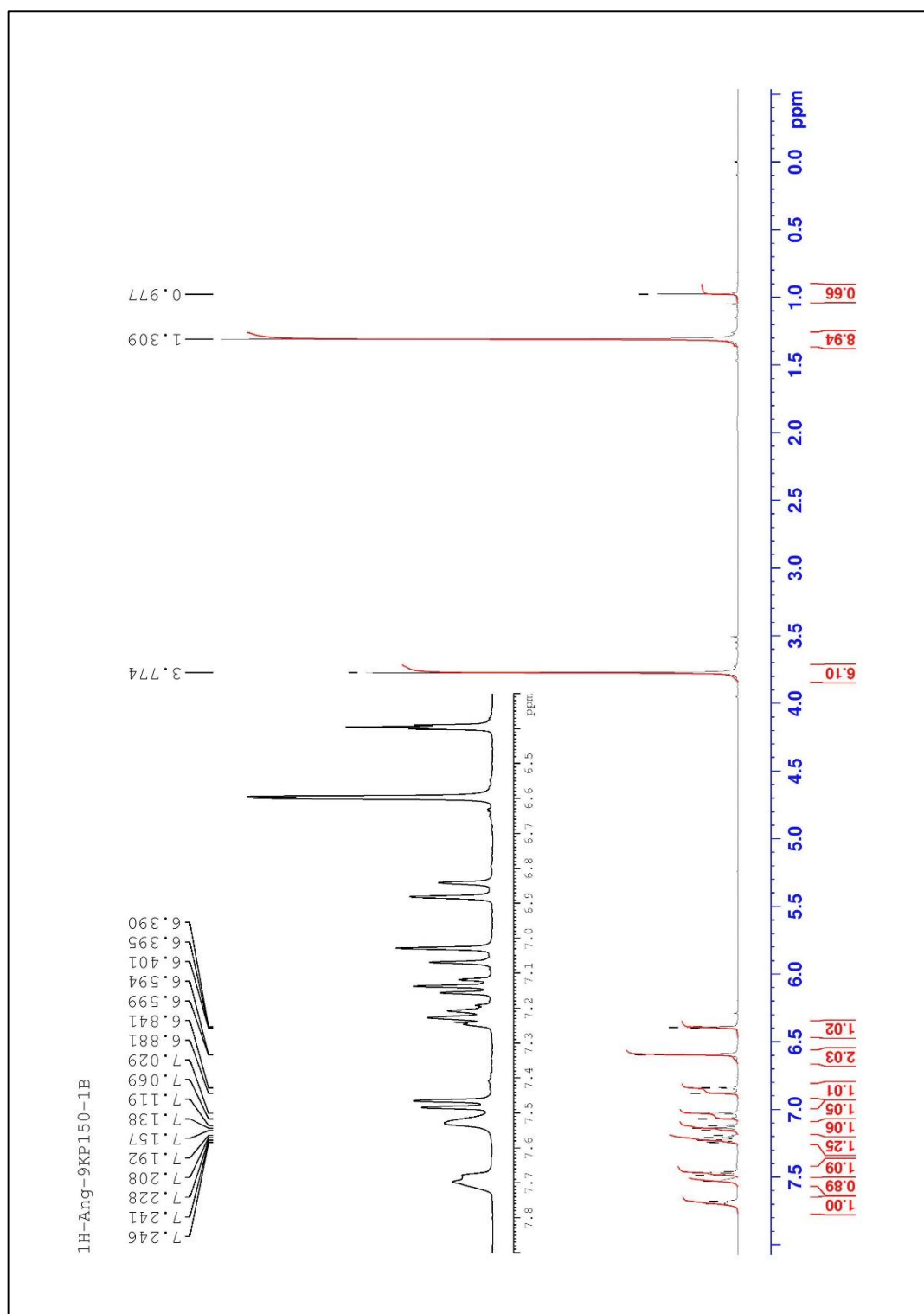


Figure A.21: ¹H spectrum (CDCl₃, 400 MHz) of **2.11**

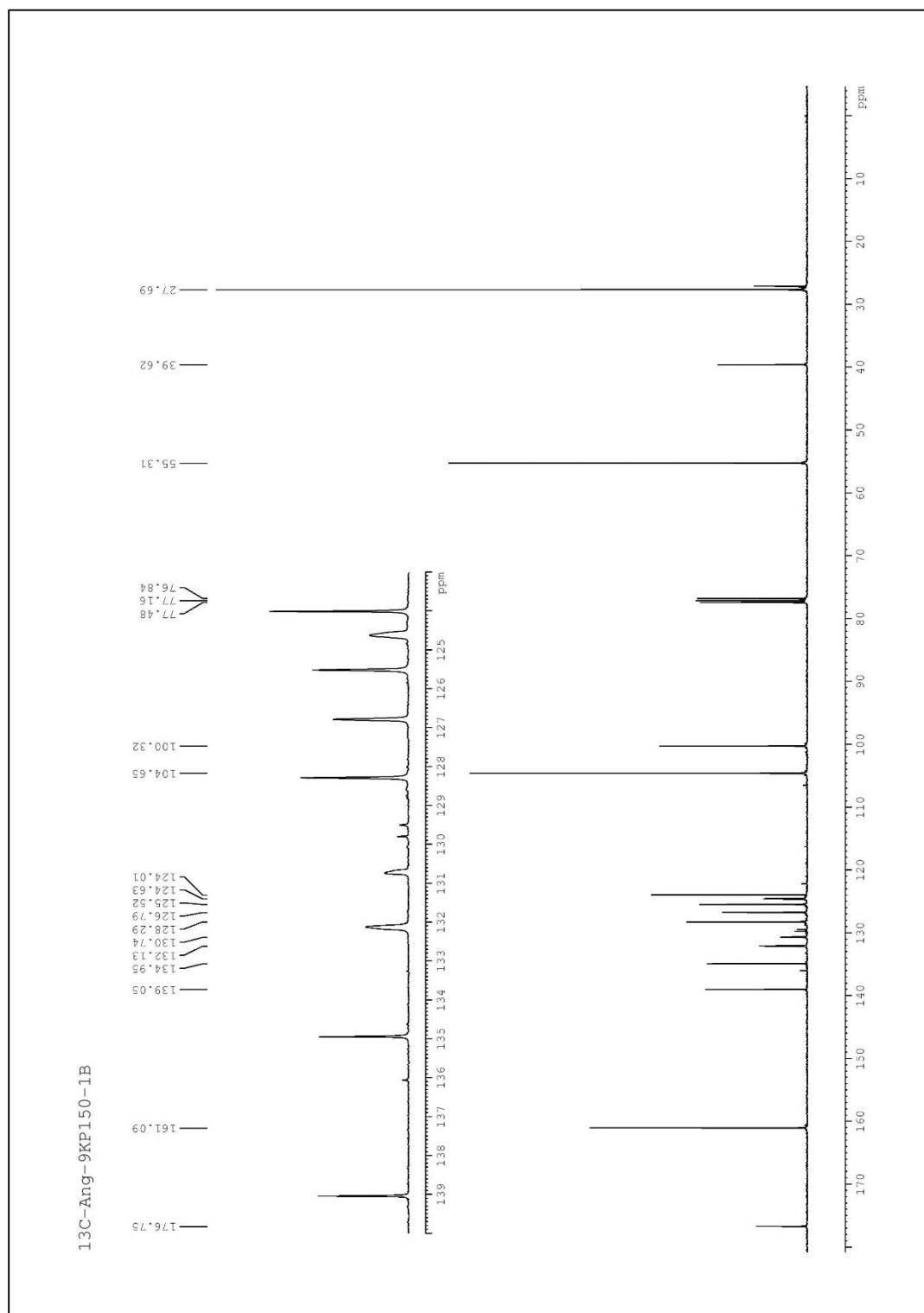


Figure A.22: ¹³C spectrum (CDCl₃, 100 MHz) of **2.11**

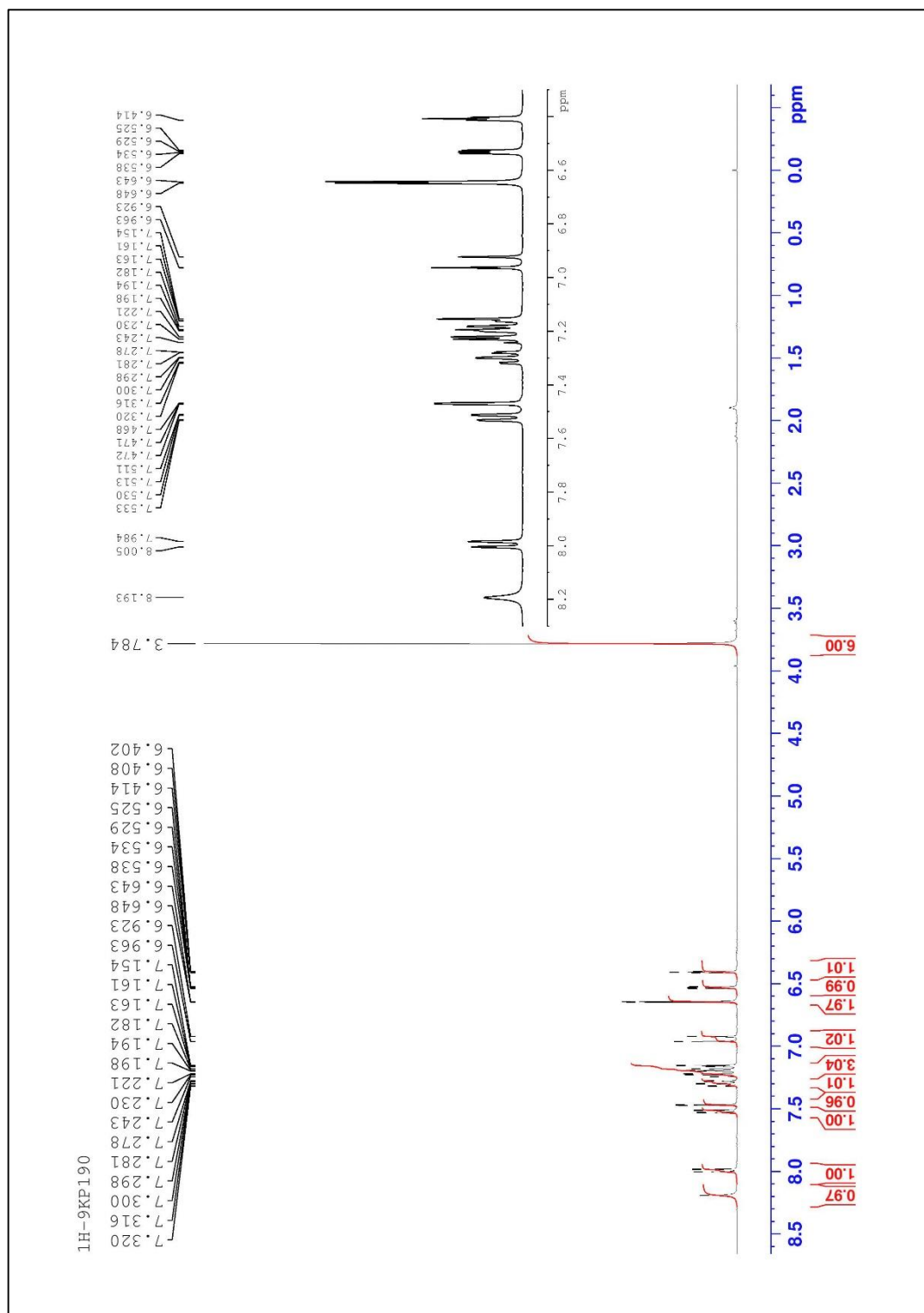


Figure A.23: ¹H spectrum (CDCl₃, 400 MHz) of **2.12**

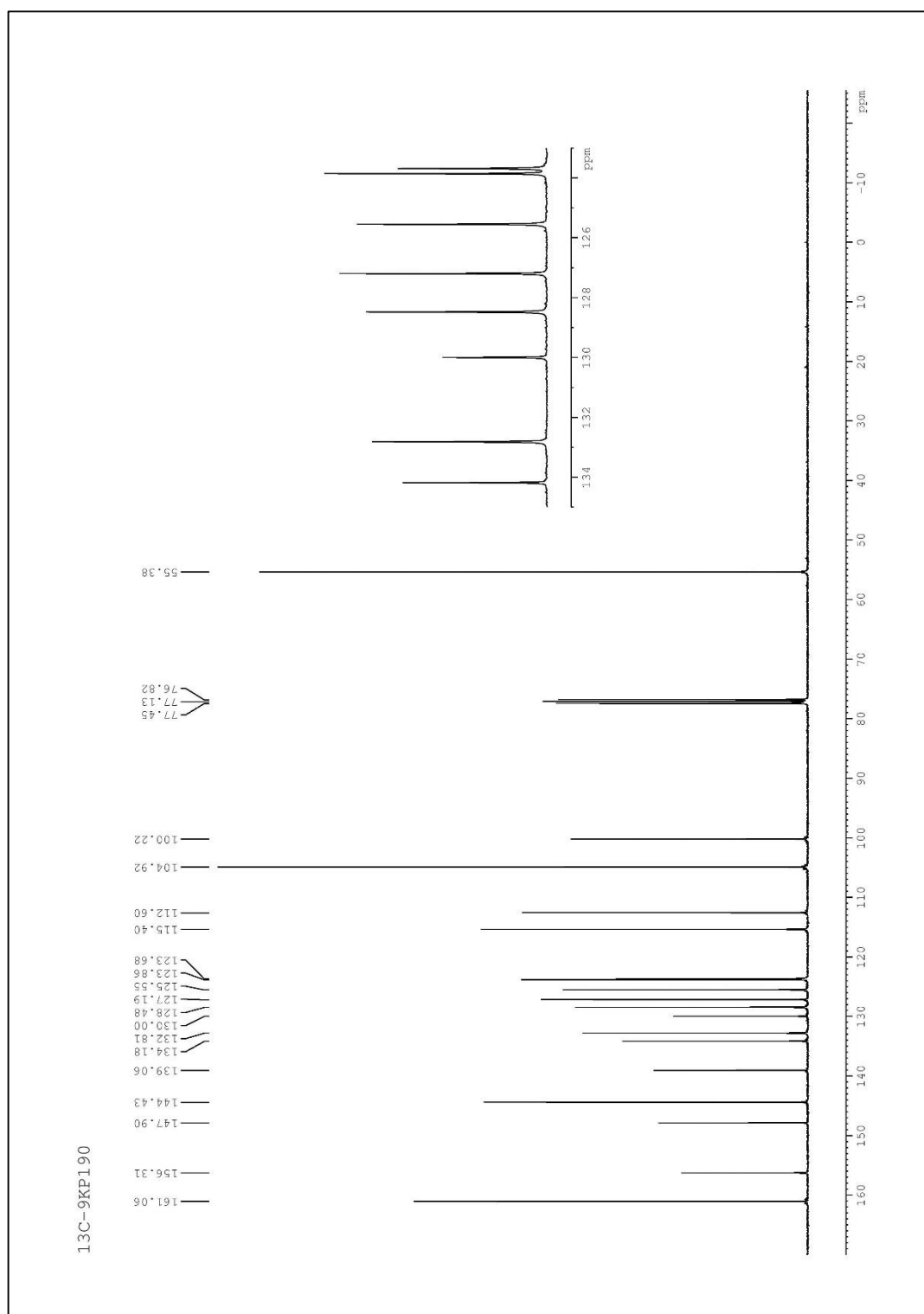


Figure A.24: ¹³C spectrum (CDCl₃, 100 MHz) of **2.12**

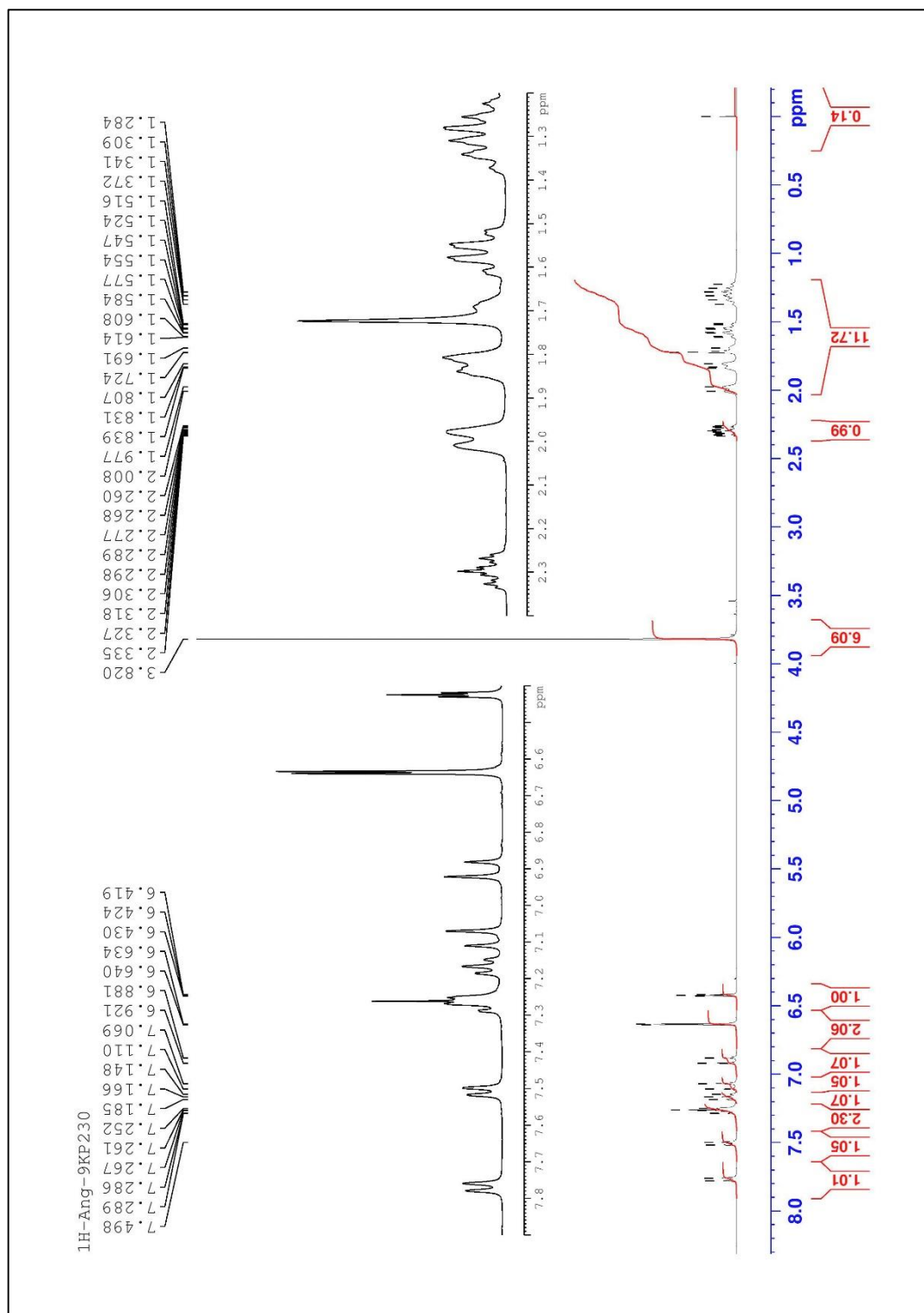


Figure A.25: ¹H spectrum (CDCl₃, 400 MHz) of **2.13**

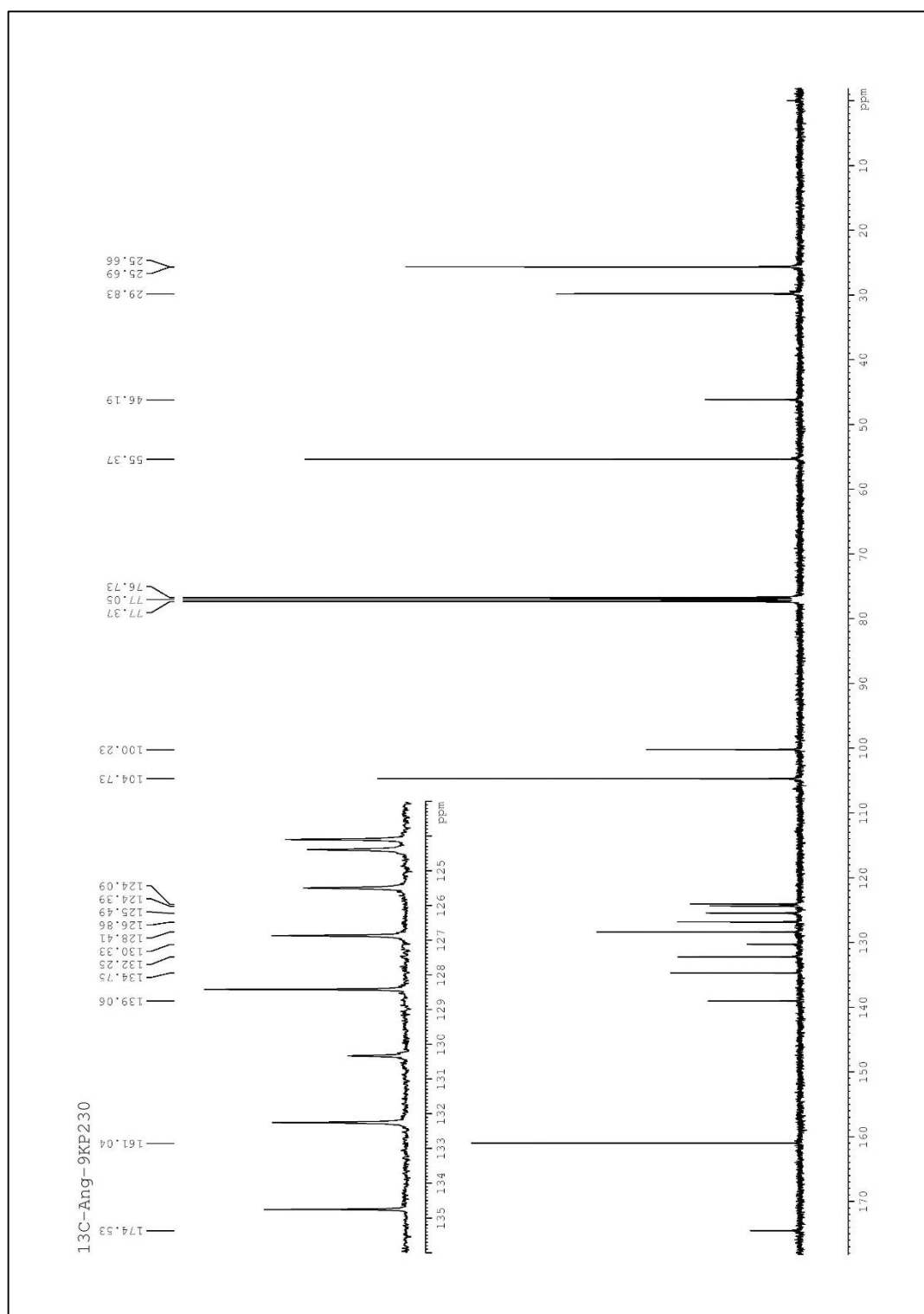


Figure A.26: ¹³C spectrum (CDCl₃, 100 MHz) of **2.13**

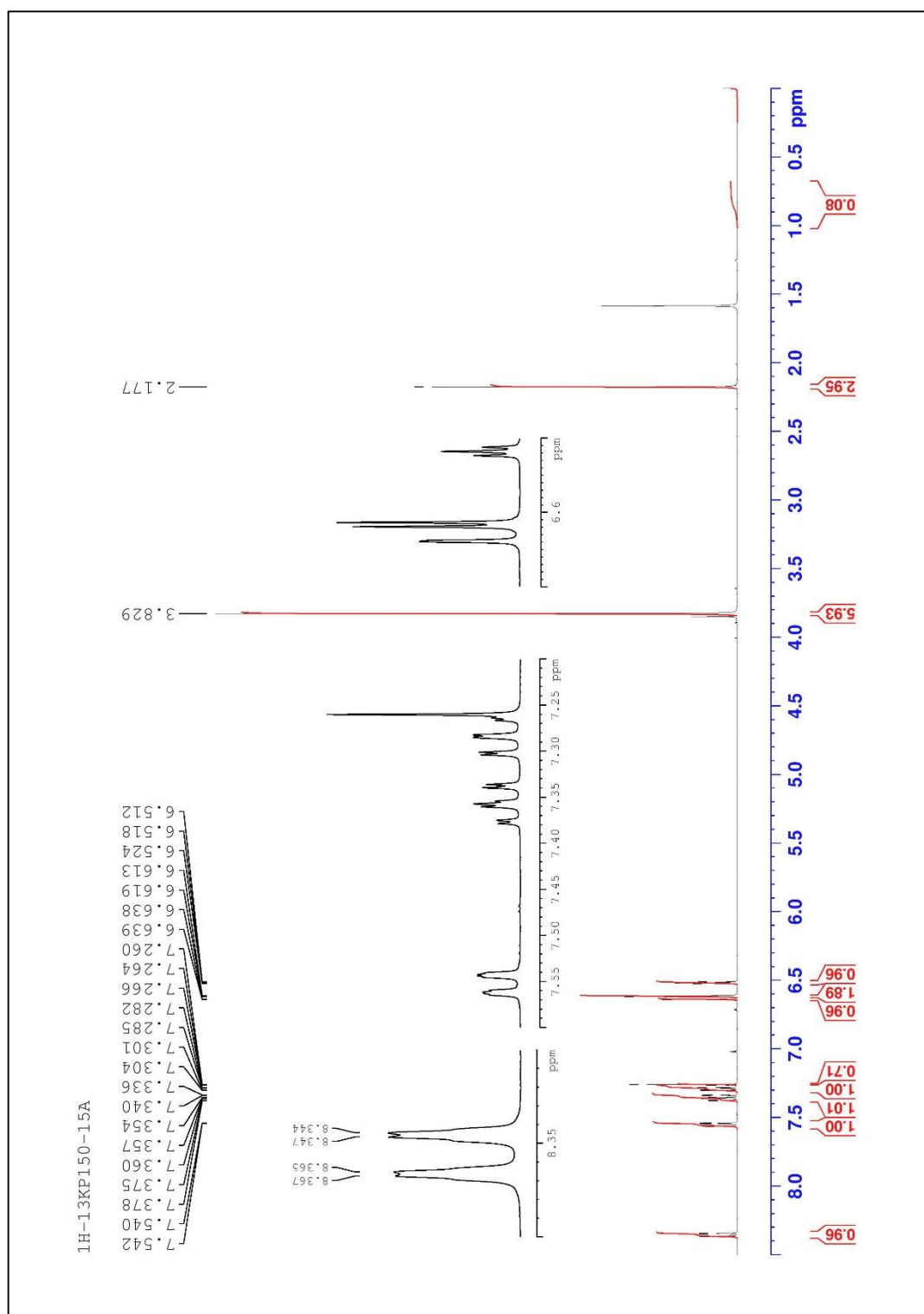


Figure A.27: ¹H spectrum (CDCl₃, 400 MHz) of **2.14**

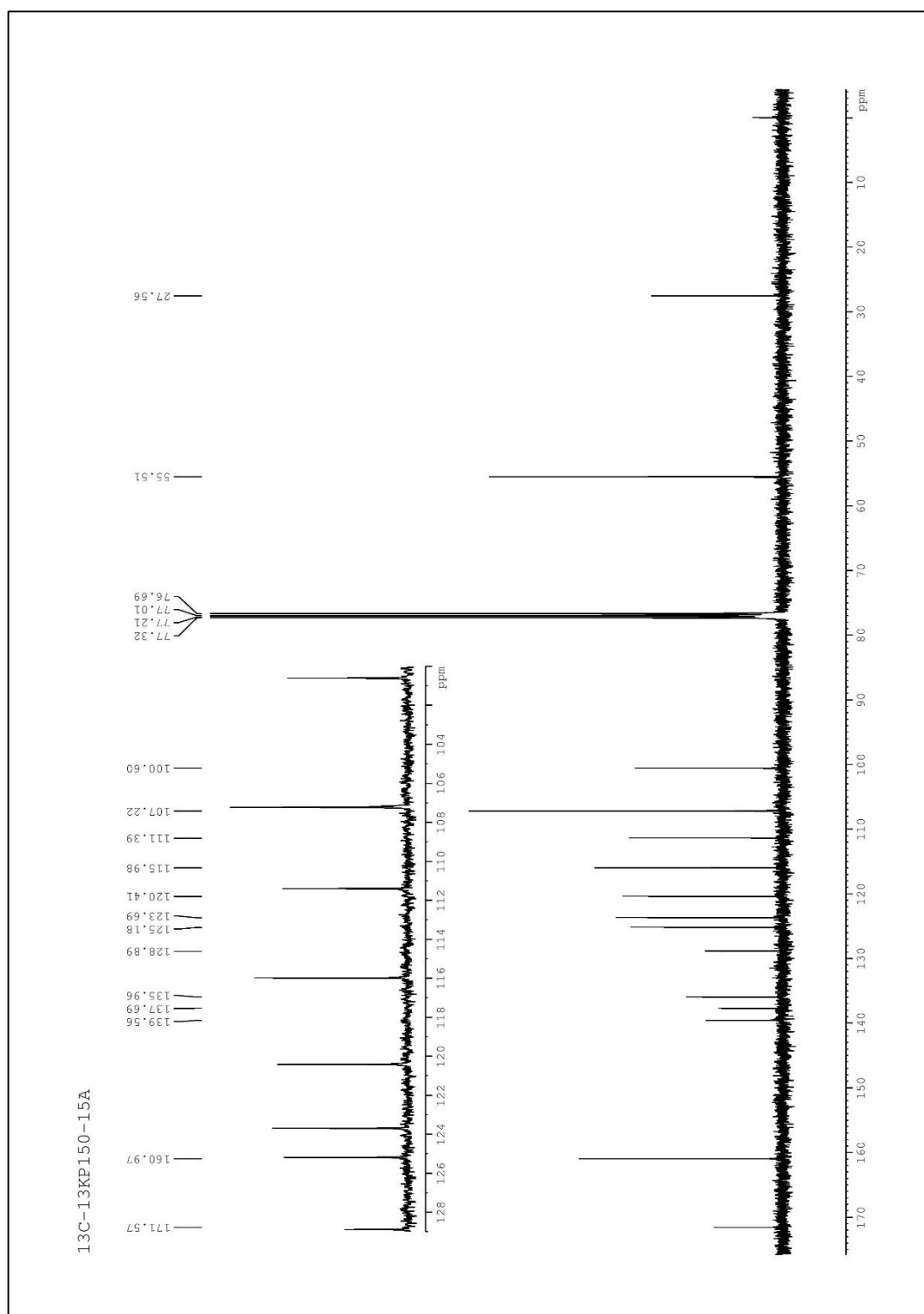


Figure A.28: ^{13}C spectrum (CDCl_3 , 100 MHz) of **2.14**

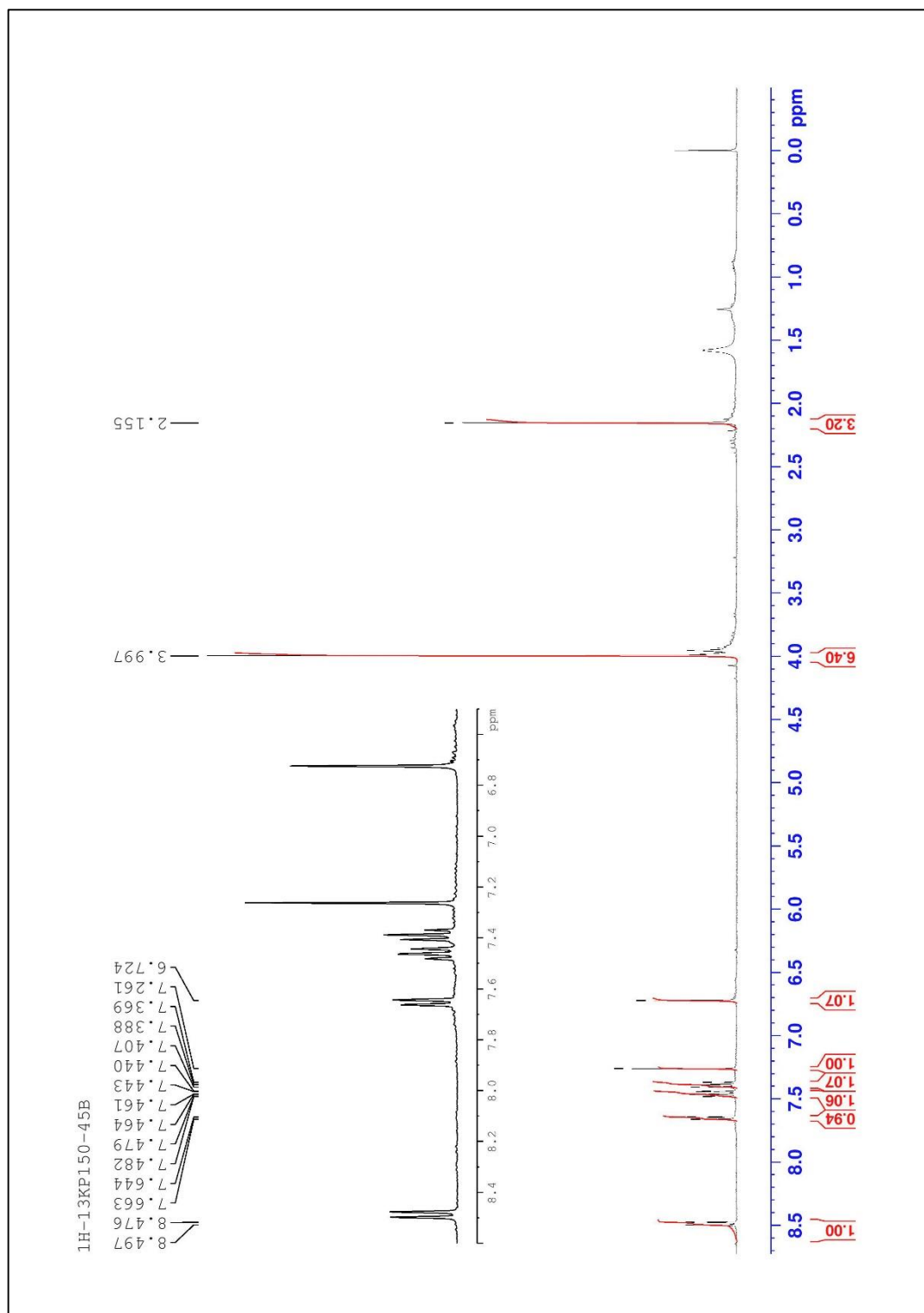


Figure A.29: ¹H spectrum (CDCl₃, 400 MHz) of **2.15**

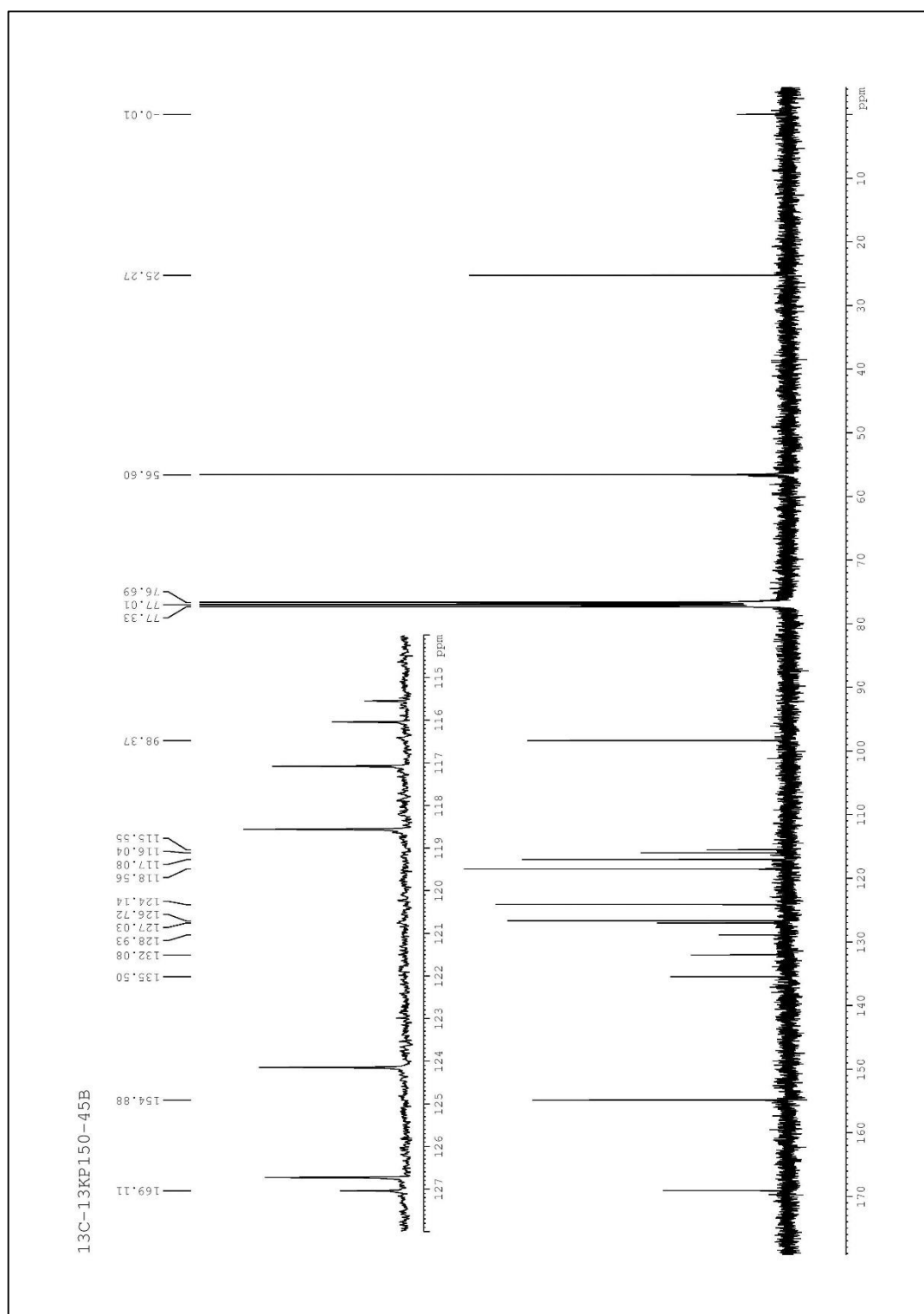


Figure A.30: ^{13}C spectrum (CDCl_3 , 100 MHz) of **2.15**

